

Considerations for Measuring and Monitoring Thermal Stress During Infancy

Mohammad Fauzan Bin Maideen

Master of Physiotherapy (Paediatric Physiotherapy), The University of Queensland, 2007

A thesis submitted in the fulfilment of the requirement for the degree of

Doctor of Philosophy

Thermal Ergonomics Laboratory

Faculty of Medicine and Health

The University of Sydney

2023

STATEMENT OF ORIGINALITY

I, Mohammad Fauzan Bin Maideen, certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I, Mohammad Fauzan Bin Maideen, certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Mohammad Fauzan Bin Maideen

Dated: 30 June 2023

Dedications

For my mum Saudah and dad Maideen, thank you for always believing in me, and in your own understated way, saying - ‘you do you, Fauzan, we will love and support you no matter what...always’ – the solace I needed in my heart.

For my mum and dad in-law, Norhayati and Selamat, your love, concern and support have been immeasurable, I am indeed blessed to be your son in-law, thank you.

For my brothers and sisters in-law, I could not have asked for a more amazing tribe who’s always got my back. This is for you too.

Truly, this thesis is dedicated to my darling wife, Safrina. We have gone through so much together in this journey, it’s unbelievable. Your unconditional love and belief in me and quietly cheering me on and nudging me forward...just too much to say...so thank you my dear. I know now what I did not know then, and I feel so complete with you by my side.

Lastly, to my children, Faris, Fadhil, Fahim, Syifa’ and Sakinah, the bringer of joy to my heart and laughter to my lips, for giving your Baba an even deeper sense of purpose and drive, for knowing when to cheer me up, for keeping me in your prayers, for brightening my days and illuminating my nights, this thesis is for you.

Acknowledgements

To my exceptional supervisor, Professor Ollie Jay.

Thank you for seeing something more in me that I just couldn't see in myself. Thank you for taking me under your wing and being the catalyst of my research adventure, patiently teaching me a new scientific language and ways of critical thinking. You have instilled in me a deep respect for this field of science, and your enthusiasm, expertise and positive mindset has left a huge impact on me.

Thank you for understanding me on a personal front, respecting my opinions, worldview and work ethic, for always being there, and congratulating my wins and hearing out my lows. You are more than a supervisor to me, and we were indeed meant to cross paths in this journey of life, for which I am indeed forever grateful.

To my outstanding co-supervisor, Dr James Smallcombe.

The completion of this journey would not have been possible without you. Your expertise, calmness, graciousness and patience is unparalleled. You have provided me with the stability that I didn't realise I was seeking and kept me on track when I needed it the most. I am indeed blessed to have you as a companion on this quest of mine to better myself as a researcher, and I sincerely thank you for that.

To the best lab mates one can ask for, thank you to all the wonderful people in the Thermal Ergonomics Laboratory family. We have connected on so many levels, and it truly went beyond just the science, the experimental trials and the putting in the hard yards supporting one another in our studies, I could not have done this without you all. There are just too many names to list since I stepped into the lab in 2016, and as I sincerely do not wish to make a faux pas of missing anyone out, you know who you are. If and when you do end up reading this, this is for you guys, thank you.

To all the NICU Nepean Hospital staff, families and babies who took part in the studies and making this possible, thank you.

Lastly, for my other family in the Discipline of Physiotherapy who has been cheering me on from the sidelines all this time and being so supportive throughout this journey, thank you.

STATEMENT ON THE IMPACT OF COVID-19

The COVID-19 pandemic has impacted this thesis, specifically the work described in Chapter 5. This experimental chapter was designed as a proof-of-concept pilot study aimed at examining the efficacy of potential infant stroller colling strategies for use in hot summer weather. The original plan was to conduct a follow-up study with human infant participants, to determine the thermo-physiological effects of the stroller cooling interventions tested in Chapter 5. Unfortunately, the COVID-19 pandemic substantially limited the opportunity to conduct face-to-face research with vulnerable human participants and, therefore, precluded the completion of this study within the time constraints of this PhD candidature. It is intended that this research will be conducted in the future to further extend the findings presented in Chapter 5.

THESIS ABSTRACT

The present thesis builds upon existing evidence and public-facing recommendations in the field of infant thermoregulation, specifically in scenarios where infants are nursed under radiant warmers in the neonatal intensive care unit (NICU), and in outdoor settings, where infants can be exposed to heat stress when transported in strollers during hot summer weather. The experimental study presented in Chapter 3 aimed to compare the suitability and level of agreement of using skin temperature measured on the neck over the carotid artery (T_{neck}), with the traditional method used currently (T_{feedback}), as a surrogate non-invasive measure of core (rectal) temperature (T_{rec}) in infants nursed under a radiant warmer. The aim of the experimental study described in Chapter 4 was to further optimize the non-invasive measurement of core temperature in NICU settings. Specially, the aim was to compare the suitability and level of agreement of potential zero heat flux skin contact temperature sites – specifically the lower back region (T_{back}) when an infant is lying in supine, and on the chest (T_{chest}) when an infant is lying in prone – with the traditional method used currently (T_{feedback}) as a surrogate measure of core temperature measured rectally (T_{rec}) in infants nursed under a radiant warmer. Finally, the experimental investigation in Chapter 5 sought to empirically determine the cooling efficacy of several low-cost stroller configurations to alleviate heat stress experienced within an infant stroller carriage in hot and moderately humid weather conditions. Together, the experimental chapters of this thesis provide empirical data which may help inform the development of improved evidence-based guidance and policy to help protect potentially vulnerable infants against the effects of thermal stress during the earliest stages of life.

PUBLICATIONS

Results culminating from Chapter 5 of this thesis which have been published in a peer reviewed journal:

Bin Maideen, M.F., Jay, O., Bongers, C., Nanan, R. & Smallcombe, J.W. (2023). Optimal low-cost cooling strategies for infant strollers during hot weather, *Ergonomics*. DOI: 10.1080/00140139.2023.2172212

Publications written during the doctoral candidature, yet not directly related to,
nor formally included within this thesis:

Morris, N.B., Chaseling, G.K., English, T., Gruss, F., **Bin Maideen, M.F.**, Capon, A. & Jay, O. (2021). Electric fan use for cooling during hot weather: a biophysical modelling study, *Lancet Planetary Health*, 5, e368-377
DOI:10.1016/S2542-5196(21)00136-4

Inoue, D.S., **Bin Maideen, M.F.**, Jiménez-Maldonado, A, & Lira, F.S. (2021). Role of neuronal guidance cues in the pathophysiology of obesity: A peripheral and central overview, *Current Pharmaceutical Design*, 27, 2512-2521.
DOI:10.2174/1381612824666210316094659

Inoue, D.S., Antunes, B.M., **Bin Maideen, M.F.** & Lira F.S. (2020). Pathophysiological features of obesity and its impact on cognition: Exercise training as a non-pharmacological approach, *Current Pharmaceutical Design*, 26(9), 916-931.
DOI: 10.2174/1381612826666200114102524

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES	11
ABBREVIATIONS	14
CHAPTER 1: THESIS INTRODUCTION AND AIMS.....	16
Introduction	17
Aims and Hypotheses	21
Introduction References	23
CHAPTER 2: REVIEW OF LITERATURE.....	27
Human heat balance and its application in infant thermoregulation.....	28
Neonatal skin and thermoregulation	33
Radiant warmers in the clinical setting.....	35
Measuring core body temperature	39
Non-invasive methods for estimating core temperature.....	41
Stroller usage and its considerations in usage in hot weather conditions.....	44
Conclusion.....	49
Literature Review References	50
CHAPTER 3: EXPERIMENTAL STUDY ONE	63
Introduction	65
Methods.....	67

Results	73
Discussion	75
Conclusion.....	78
Experimental Study One References.....	79
CHAPTER 4: BRIDGING STATEMENT.....	82
Bridging Statement References.....	84
CHAPTER 5: EXPERIMENTAL STUDY TWO.....	85
Introduction	87
Methods.....	90
Results.....	95
Discussion	100
Conclusion.....	104
Experimental Study Two References.....	105
CHAPTER 6: BRIDGING STATEMENT.....	108
Bridging Statement References.....	110
CHAPTER 7: EXPERIMENTAL STUDY THREE	111
Introduction	113
Methods.....	116
Results.....	124
Discussion	131

Conclusion.....	140
Experimental Study Three References	141
CHAPTER 8: GENERAL DISCUSSION AND THESIS CONCLUSIONS.....	146
Summary	147
Implications and future directions	149
Thesis conclusions.....	155
General Discussion and Thesis Conclusions References	156
THESIS BIBLIOGRAPHY	158
APPENDIX A: Attestation of Statement for Chapter 3.....	175
APPENDIX B: Attestation of Statement for Chapter 5.....	176
APPENDIX C: Attestation of Statement for Chapter 7	177
APPENDIX D: Ethical Approval For Experimental Study One and Two	178
APPENDIX E: Public Engagement and Media Coverage related to Experimental Study Three	185
APPENDIX F: Publications Written During the Doctoral Candidature, yet not related to, nor formally included within this thesis.....	194

LIST OF TABLES AND FIGURES

Chapter 1: Thesis Introduction and Aims

Figure 1: A) After delivery, a newborn infant born prematurely is susceptible to hypothermia amidst exposure to the cold ambient hospital environment. The infant may be nursed under a radiant warmer in the neonatal intensive care unit (NICU) to mitigate excessive heat loss. Chapters 3 and 5 (experimental studies 1 and 2) of this thesis aim to investigate optimal non-invasive temperature monitoring methods that can best reflect infant core body temperature whilst under the radiant warmer. B) Once clinically stable, the infant then graduates from the NICU, a tightly controlled indoor environment, to natural environments, including hot outdoor conditions, as part of interactions of daily living. C) A means of transporting the infant outdoors is with a stroller. With the infant now exposed to the outdoors, if the ambient temperature is higher than the infant's skin temperature, the infant is now more susceptible to body temperature rises with dry heat gain as heat energy flows down from a higher to lower temperature gradient. This may lead to excessive thermal stress for the infant in the stroller. Chapter 7 (experimental study 3) of this thesis thus aims to empirically measure how hot the stroller can get in hot outdoor environments as well as to investigate cost-efficient interventions to cool down the stroller accordingly.

Chapter 2: Review of Literature

Figure 1: Radiant warmer set up. The doll is placed in the centre of the mattress, to replicate an infant nursed under the radiant warmer.

Chapter 3: Experimental Study One

Table 1: Infant characteristics.

Figure 1: Skin sensor placement sites on an infant participant.

Figure 2: Positioning of an infant participant under the radiant warmer.

Figure 3: Left: Bland-Altman plots illustrating the mean bias (solid line) and 95% confidence intervals (± 1.96 s.d.: dotted lines) for measured rectal temperature (T_{rec}) vs the difference between rectal temperature and skin temperature measured on the neck (T_{neck}) and the servo-feedback temperature sensor of the radiant warmer positioned at the mid-axillary line ($T_{feedback}$). The red band indicates the a priori acceptable limits of agreement

(± 0.5 °C) for estimating core temperature. **Right:** Simple regression analysis of the relationship between absolute T_{neck} , $T_{feedback}$ with absolute T_{rec} .

Chapter 4: Experimental Study Two

Table 1: Infant characteristics.

Table 2: Mean bias and 95% limits of agreement (LoA) for estimates of core body temperature (compared with rectal temperature) derived from different skin temperature sites in the supine and prone positions.

Figure 1: Schematic diagram illustrating the skin sensor placements on the infant. **A. Supine:** 1 – $T_{forehead}$ (centre of forehead); 2 – T_{chest} (centre of sternum); 3 – $T_{abdomen}$ (upper abdomen); 4 – T_{arm} – (upper anterior arm); 5 – $T_{feedback}$ (mid-axillary line at the lateral aspect of trunk); 6 – T_{thigh} (anterior thigh); 7. T_{foot} – (dorsum of foot). **B. Prone:** 8 – T_{back} (L4-L5 region at the paraspinal aspect).

Figure 2: Left: Bland-Altman plots illustrating the mean bias (solid line) and 95% confidence intervals (± 1.96 s.d.: dotted lines) for measured rectal temperature (T_{rec}) vs the difference between rectal temperature and skin temperature measured on the back ($T_{back(contact)}$) and the servo-feedback temperature sensor of the radiant warmer positioned at the mid-axillary line (in supine position). The red band indicates the a priori acceptable limits of agreement (± 0.5 °C) for estimating core temperature. **Right:** Simple regression analysis of the relationship between absolute $T_{back(contact)}$, $T_{feedback}$ with absolute T_{rec} in the supine position.

Figure 3: Left: Bland-Altman plots illustrating the mean bias (solid line) and 95% confidence intervals (± 1.96 s.d.: dotted lines) for measured rectal temperature (T_{rec}) vs the difference between rectal temperature and the skin temperature measured on the chest ($T_{chest(contact)}$) and the servo-feedback temperature sensor of the radiant warmer positioned at the mid-axillary line (in prone position). The red band indicates the a priori acceptable limits of agreement (± 0.5 °C) for estimating core temperature. **Right:** Simple regression analysis of the relationship between absolute $T_{chest(contact)}$, $T_{feedback}$ with absolute T_{rec} in the prone position.

Figure 4: Individual participant examples of the temporal $T_{back(contact)}$ vs T_{rec} temperature response during experimental observation.

Chapter 5: Experimental Study Three

Table 1: Summary description of cooling interventions (see Figure 3 for images).

Table 2. The mean (mean of 16 separate experimental observations) end of trial in-stroller and

outside ambient environmental conditions and the mean differences observed between in-stroller vs outside for each stroller configuration.

Figure 1: Schematic diagram of pre-determined 72.5 m route along which the stroller was pushed during each 20-min intervention. The red dashed lines indicate the stroller route, the red arrows indicate the direction, the hatched circle indicates the location of the environmental measuring unit, placed on the tarmac of the nearby parking lot unobstructed.

Figure 2: In-stroller thermistors and Kestrel 5400-unit placement within the purpose-built wire frame. Numbers 1–4 indicate individual thermistor placement relative to a simulated infant's body segments (i.e. head, chest, abdomen, and legs). Numbers 5 and 6 indicate the thermistor placement measuring the temperature in the upper portion of the stroller carriage space, close to the canopy. The orange icon indicates the location of the Kestrel 5400 unit, placed near the centre of the wire frame, which was suspended 15 cm above the stroller seat surface.

Figure 3: The tested stroller cooling interventions. All fabric drapings were secured using plastic clothes pegs, ensuring that there were no gaps present. For illustrative purposes, the drapings of interventions E and F were raised on one side to display the position of the battery-operated fan.

Figure 4. The mean (minute averaged data) in-stroller environmental conditions for each stroller cooling intervention. Due to the number of interventions presented, error bars have been omitted for clarity.

Figure 5. The mean end-trial difference between the in-stroller vs outside air temperature (T_a) and WBGT, expressed relative to the difference observed during Closed Stroller Control. T1–T6 represent the mean relative ΔT_a for each of the six thermistors located in the stroller chamber.

*Significantly lower than Closed Stroller Control ($p < 0.05$). †Significantly higher than Closed Stroller Control ($p < 0.05$).

ABBREVIATIONS

Term	Abbreviation
Abdominal temperature	T_{abdomen}
Ambient temperature	T_a
Ambient water vapour partial pressure	p_2
Analysis of variance	ANOVA
Arm temperature	T_{arm}
Bureau of Meteorology	BOM
Black globe temperature	T_{globe}
Centimetre	cm
Change in ambient temperature	ΔT_a
Chest temperature	T_{chest}
Conductive heat transfer	K
Temperature of contact skin site on the back	$T_{\text{back}(\text{contact})}$
Temperature of contact skin site on the chest	$T_{\text{chest}(\text{contact})}$
Convective heat transfer	C
Degrees Celsius	$^{\circ}\text{C}$
Dry bulb temperature	T_{db}
Environmental Measuring Unit	EMU
Evaporative heat loss	E
Evaporative heat transfer coefficient	h_e
Feedback temperature	T_{feedback}
Figure	Fig.
Foot temperature	T_{foot}
Forehead temperature	T_{forehead}
General Electric	GE
Gram	g
Heat production	H_{prod}
Hours	h
Intensive care unit	ICU
joules per gram	J/g
joules per second	$\text{j}\cdot\text{s}^{-1}$
Kilogram	kg
Kilojoule	kJ
Limits of Agreement	LoA
Low birth weight	LBW
Lower back temperature	T_{back}
Maximal oxygen consumption	$\text{VO}_{2\text{max}}$
Mean skin temperature	T_{sk}
Metabolic Energy Expenditure	M

Term	Abbreviation
Metabolic Heat Production	M-W
Metres	m
Metres per second	m/s
Metres squared	m ²
Millimetres	mm
Millimetres mercury	mmHg
Milliseconds	ms
Minutes	min
Natural wet bulb temperature	T _{nwb}
Net heat storage	S
Neonatal Intensive Care Unit	NICU
Post meridiem	pm
Radiative heat transfer	R
Rectal temperature	T _{rec}
Relative humidity	RH
Respiratory exchange ratio	RER
Seconds	s
Skin temperature over carotid artery	T _{neck}
Skin surface water vapour partial pressure	p ₁
Standard deviation	s.d.
Sudden infant death syndrome	SIDS
Temperature gradient	ΔT
Thigh temperature	T _{thigh}
Ultraviolet	UV
Watts	W
Wet bulb temperature	T _{wb}
Wet Bulb Globe Temperature	WBGT
World Health Organisation	WHO

CHAPTER 1: THESIS INTRODUCTION AND AIMS

Introduction

It is well established that thermoregulation is a vital physiological process that is linked to the survival of the newborn [1] and as homeotherms, these infants must keep their deep internal body temperature within a particular range to optimize physiological functions [2, 3]. Maintaining normothermia, or a normal core body temperature between 36.5°C and 37.5°C, by balancing heat loss and heat gain, is therefore critical to the infant's wellbeing [2]. After delivery, an infant is susceptible to sensible (dry) and insensible (evaporation) heat loss due to the high body surface area to mass ratio, an immature epidermal barrier, lack of subcutaneous fat insulation, while also having a low capacity to produce metabolic heat by shivering, and an inability to exhibit behavioural thermoregulatory responses, all of which can lead to hypothermia [4-6]. Hypothermia is defined as the infant's core body temperature falling below 36.5°C and is listed by the World Health Organisation as one of the leading causes of infant mortality, especially in low-resource countries [7, 8]. The World Health Organisation further categorized the body temperature ranges for mild hypothermia (cold stress) as 36°C-36.5°C; moderate hypothermia as 32°C-36°C, and severe hypothermia as less than 32°C [7]. Infants who are born prematurely (less than 37 weeks of gestation) and with low birth weights (less than 2500g) are even more susceptible to hypothermia due to an immature central nervous system and require constant observation and additional nursing care to prevent hypothermia [2].

To mitigate excessive heat loss post-delivery, one strategy employed in the delivery suites, nurseries, and neonatal intensive care units (NICU) is the use of the radiant warmer [4, 9]. Radiant warmers are purpose-built devices that provide radiant heat to the infant via a radiant heat source, i.e., radiant lamp that is positioned overhead while the infant is lying on a mattress in an open cot setting [10]. This radiant heat transfer mitigates infant cold stress by reducing heat loss to the

environment and reversing it to radiant heat gain instead [5]. The heat output of the radiant warmer is controlled by a servocontrol mode, an electronic feedback system that serves as a thermostat to maintain a constant temperature based on the input from a skin thermistor probe, usually placed over the mid-axillary line or over the abdomen, also known as T_{feedback} [11, 12]. Whilst it is intended that T_{feedback} serves as a surrogate method to measure core body temperature in the infant, recent studies had determined that the present T_{feedback} system results in transient, cyclical bouts of heat debt and heat storage leading to fluctuations in deep core temperature and infant physiological strain, with the potential to result in accidental bouts of overheating [13, 14]. It has also been established that large variations in local skin temperature are observed despite the tight regulation of T_{feedback} , with poor agreement between T_{feedback} and deep core temperature measured rectally [15]. Another study demonstrated that a feasible non-invasive approach may be a temperature sensor placed on the skin of the neck (T_{neck}) over the carotid artery [16]. This study established that T_{neck} was a more precise non-invasive core temperature estimation location than the conventional T_{feedback} measurement site in paediatric patients under general anaesthesia during elective surgery. This T_{neck} measure could serve as a better feedback temperature for controlling radiant warmer output, and as an improved method for regulating radiant heat output is required, this forms the primary focus of investigation in Chapter 3.

Zero heat flux thermometry is another approach that has been adopted as a non-invasive surrogate measure for core temperature. It is a technique of estimating deep core temperature based on the idea that the gradient between deep core temperature and skin surface temperature will go in the direction of zero if heat loss from the body's skin surface is reduced to zero with adequate thermal insulation on the skin. In doing so, it is assumed that the surface temperature of the skin will then equalise with its deep core temperature [17-19]. It can be inferred that the gradient

between a newborn's skin and internal organs is already less than that of an adult due to the decreased depth of the body's tissues and the absence of subcutaneous fat, therefore making the zero-heat flux approach a workable concept in the infant population [20].

Traditionally, this approach required the use of specialised zero heat flux skin thermometers, and according to several studies that evaluated the use of the zero-heat flux approach in intensive care and surgical settings, these thermometers were sufficient in replacing invasive thermometry methods [21-23]. However, due to the cost and accessibility, a more practical approach needed to be adopted. Several studies had looked into covering a standard skin temperature probe with a suitable insulatory material, or via direct contact of the skin surface onto an insulating material e.g., mattress [24, 25] in incubators, in which the air temperature within these devices is controlled and demonstrated its efficacy. However, as this approach has not been explored in infants nursed over long durations in an open radiant warmer, its suitability as a more accurate non-invasive estimation of infant core temperature is investigated in Chapter 5.

Due to the high body surface area to mass ratio in infants, when the ambient temperature is higher than skin temperature, infants are more susceptible to body temperature rises with dry heat gain as heat energy flows down from a higher to lower temperature gradient. This can lead to excessive heat stress in hot outdoor environments during activities of daily living, such as being transported in a stroller. It had been previously reported that internal stroller temperatures can increase up to 37°C when left in a stationary position with a cloth covering, in an open-air setting in summer [26]. However, the methods of ascertaining the temperature and conditions in the stroller carriage were not explained, and the implausibility of leaving a static stroller in hot weather unattended for 90 minutes also makes the finding irrelevant for daily application. Nevertheless, this has been part of publicly disseminated advice and guidance [27-29] which is unfortunately not

based on empirical evidence. More importantly, efficacious strategies to cool a stroller have not yet been identified. Studies have shown that cooling methods via fan use and strategies employing evaporative cooling mechanisms were effective in the adult population [30-32], however this has not been determined in stroller use in hot outdoor environments to date. With this gap in the literature, the experimental study described in Chapter 7 aim to explore interventions to cool a stroller in hot weather that were low-cost and accessible to parents and caregivers. Figure 1 provides a visual representation of the overarching theme of this thesis.

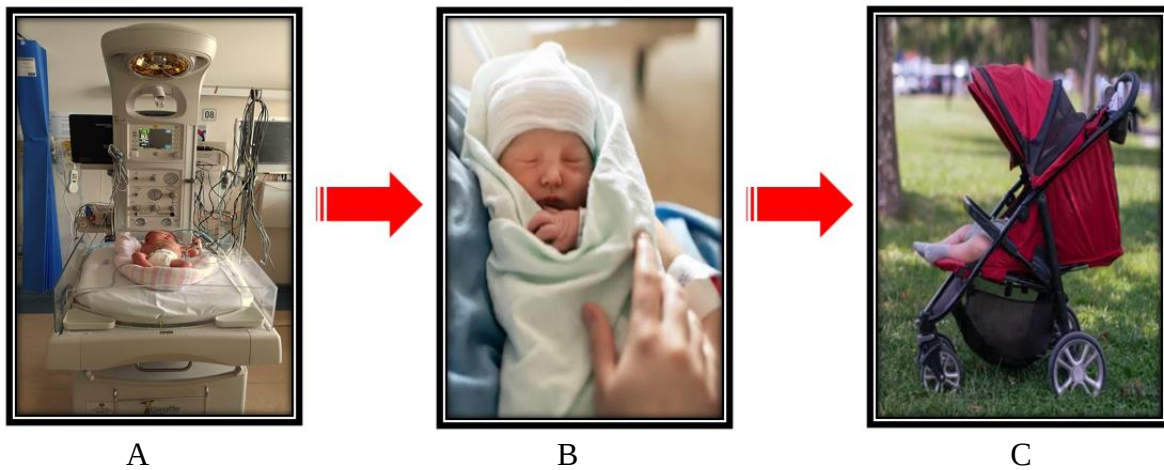


Figure 1. A) After delivery, a newborn infant born prematurely is susceptible to hypothermia amidst exposure to the cold ambient hospital environment. The infant may be nursed under a radiant warmer in the neonatal intensive care unit (NICU) to mitigate excessive heat loss. Chapters 3 and 5 (experimental studies 1 and 2) of this thesis aim to investigate optimal non-invasive temperature monitoring methods that can best reflect infant core body temperature whilst under the radiant warmer. B) Once clinically stable, the infant then graduates from the NICU, a tightly controlled indoor environment, to natural environments, including hot outdoor conditions, as part of interactions of daily living. C) A common means of transporting the infant outdoors is with a stroller. With the infant now exposed to the outdoors, if the ambient temperature is higher than the infant's skin temperature, the infant is now more susceptible to body temperature rises due to an increase in dry heat gain as heat energy flows down from a higher to lower temperature gradient. This may lead to excessive thermal stress for the infant in the stroller. Chapter 7 (experimental study 3) of this thesis thus aims to empirically measure how hot the stroller can get in hot outdoor environments as well as to investigate effective low-cost interventions to cool the stroller carriage during hot weather.

Aims and Hypotheses

The specific aims and hypotheses governing each of the original research chapters in this thesis are:

Experimental Study One (Chapter 3)

The aim of this chapter was to compare the suitability and level of agreement in using a skin site on the neck over the carotid artery (T_{neck}) in comparison to the current standard method (T_{feedback}), which has previously been shown to be a promising method in anaesthetised children undergoing elective general surgery, as a surrogate measure of an invasive core (rectal) temperature (T_{rec}) in infants nursed under a radiant warmer.

It was hypothesized that the level of agreement with T_{rec} would be superior with T_{neck} compared to T_{feedback} .

Experimental Study Two (Chapter 5)

The aim of this chapter was to compare the suitability and level of agreement of potential skin contact temperature sites, specifically the lower back region (T_{back}) when an infant is lying in supine, and on the chest (T_{chest}) when an infant is lying in prone, in comparison to the current standard method (T_{feedback}), as a surrogate measure of core temperature measured rectally (T_{rec}) in infants nursed under a radiant warmer.

It was hypothesized that the level of agreement with T_{rec} would be superior with T_{back} (when supine) and T_{chest} (when prone) compared to T_{feedback} .

Experimental Study Three (*Chapter 7*)

The aim of this chapter was to empirically examine the cooling efficacy of eight different low-cost stroller configurations, to reduce the heat stress experienced inside an infant stroller carriage in hot and moderately humid weather conditions. These eight configurations are: (i) the canopy closed (which served as the standard-practice control intervention); (ii) a commercially available battery operated clip-on fan; (iii) a white muslin cloth draped over the front of the carriage; (iv) a flannelette cloth (made of polyester) draped over the front of the carriage; (v) a combination of muslin cloth and clip-on fan; (vi) a combination of flannelette cloth and clip-on fan; (vii) a completely moistened muslin cloth draping; and (viii) a combination of a completely moistened muslin cloth draping and clip-on fan.

It was hypothesized that the stroller configurations that incorporated evaporative cooling techniques would reduce the heat stress severity experienced inside the stroller carriage, whereas those that utilised a dry material covering would exacerbate the level of in-stroller heat stress.

Introduction References

1. Silverman, W.A., J.W. Fertig, and A.P. Berger, *The influence of the thermal environment upon the survival of newly born premature infants*. Pediatrics, 1958. **22**(5): p. 876-886.
2. Hackman, P., *Recognizing and Understanding the Cold-Stressed Term Infant*. Neonatal network, 2001. **20**(8): p. 35-41.
3. LeBlanc, M.H., *Thermoregulation: Incubators, Radiant Warmers, Artificial Skins, and Body Hoods*. Clinics in Perinatology, 1991. **18**(3): p. 403-422.
4. Watkinson, M., *Temperature control of premature infants in the delivery room*. Clinics in perinatology, 2006. **33**(1): p. 43.
5. Bell, E.F., *Infant incubators and radiant warmers*. Early Human Development, 1983. **8**(3): p. 351-375.
6. Székely, M. and J. Garai, *Thermoregulation and age*. Handbook of clinical neurology, 2018. **156**: p. 377-395.
7. WHO, *Thermal Protection of the Newborn: a practical guide*. 1997, World Health Organisation: Geneva.
8. Lunze, K., et al., *The global burden of neonatal hypothermia: systematic review of a major challenge for newborn survival*. BMC medicine, 2013. **11**(1): p. 24-24.
9. Laptook, A.R. and M. Watkinson, *Temperature management in the delivery room*. Seminars in Fetal and Neonatal Medicine, 2008. **13**(6): p. 383-391.
10. Wheldon, A.E. and N. Rutter, *The heat balance of small babies nursed in incubators and under radiant warmers*. Early Human Development, 1982. **6**: p. 131-143.

11. Hunter New England Local Health District, *Local Guidelines: Thermoregulation of the neonate in NICU*. 2015, New South Wales Health, Australia: John Hunter Children's Hospital.
12. Joseph, R.A., S. Derstine, and M. Killian, *Ideal Site for Skin Temperature Probe Placement on Infants in the NICU: A Review of Literature*. *Adv Neonatal Care*, 2017. **17**(2): p. 114-122.
13. Molgat-Seon, Y., et al., *Accidental overheating of a newborn under an infant radiant warmer: a lesson for future use*. *Journal of Perinatology*, 2013. **33**(9): p. 738-9.
14. Molgat-Seon, Y., et al., *Assessing neonatal heat balance and physiological strain in newborn infants nursed under radiant warmers in intensive care with fentanyl sedation*. *European Journal of Applied Physiology*, 2014. **114**(12): p. 2539-49.
15. Chaseling, G.K., et al., *Body temperature mapping in critically ill newborn infants nursed under radiant warmers during intensive care*. *Journal of Perinatology*, 2016. **36**(7): p. 540-3.
16. Jay, O., et al., *Skin temperature over the carotid artery provides an accurate noninvasive estimation of core temperature in infants and young children during general anesthesia*. *Paediatric Anaesthesia*, 2013. **23**(12): p. 1109-16.
17. Fox, R.H., et al., *A New Method for Monitoring Deep Body Temperature from the Skin Surface*. *Clinical Science and Molecular Medicine*, 1973. **44**(1): p. 81-86.
18. Togwa, T., et al., *A modified internal temperature measurement device*. *Medical & Biological Engineering*, 1976. **14**(3): p. 361-364.
19. Yamakage, M. and A. Namiki, *Deep temperature monitoring using a zero-heat-flow method*. *Journal of Anesthesia*, 2003. **17**: p. 108-115.

20. Hey, E.N. and G. Katz, *The Range of Thermal Insulation in the Tissues of the New Born Baby*. Journal of Physiology, 1970. **207**: p. 667-681.
21. Kimberger, O., et al., *Accuracy and precision of a novel non-invasive core thermometer*. British Journal of Anaesthesia, 2009. **103**(2): p. 226-31.
22. Eshraghi, Y., et al., *An Evaluation of a Zero-Heat-Flux Cutaneous Thermometer in Cardiac Surgical Patients*. Anesthesia and Analgesia, 2014. **119**: p. 543-9.
23. Dahyot-Fizelier, C., et al., *Accuracy of Zero-Heat-Flux Cutaneous Temperature in Intensive Care Adults*. Critical Care Medicine, 2017. **45**: p. e715–e717.
24. Dollberg, S., et al., *Effect of insulated skin probes to increase skin-to-environmental temperature gradients of preterm infants cared for in convective incubators*. The Journal of Pediatrics, 1994. **124**(5): p. 799-801.
25. van der Spek, R.D., R.A. van Lingen, and D. van Zoeren-Grobbe, *Body temperature measurement in VLBW infants by continuous skin measurement is a good or even better alternative than continuous rectal measurement*. Acta Paediatrica, 2009. **98**(2): p. 282-5.
26. Holmberg, H. *Swedes risk infants' lives by covering up prams*. . The Local 2014; Available from: <https://www.thelocal.se/20140711/swedes-risk-infants-lives-by-covering-up-prams>.
27. *National Health Service (NHS). Keeping your baby safe in the sun*. 2021; Available from: <https://www.nhs.uk/conditions/baby/first-aid-and-safety/safety/safety-in-the-sun/>.
28. *NSW Health. Babies and children in the heat*. 2022; Available from: <https://www.health.nsw.gov.au/environment/beattheheat/Pages/babies-children-hot-weather.aspx>.
29. Christian, N. *Heatwave warning: Common pram habit could be potentially fatal for babies and young kids*. 2019; Available from:

<https://thewest.com.au/lifestyle/parenting/heatwave-warning-common-pram-habit-could-be-potentially-fatal-for-babies-and-young-kids-ng-81b054ca62b17dd6cd7c6b651c14a6a9>.

30. Morris, N.B., et al., *Electric fan use for cooling during hot weather: a biophysical modelling study*. The Lancet: Planetary Health, 2021. 5(6): p. e368-e377.
31. Song, W., F. Wang, and C. Zhang, *Intermittent wetting clothing as a cooling strategy for body heat strain alleviation of vulnerable populations during a severe heatwave incident*. Journal of Thermal Biology, 2019. 79: p. 33-41.
32. Cramer, M.N., et al., *Keeping older individuals cool in hot and moderately humid conditions: wetted clothing with and without an electric fan*. Journal of Applied Physiology 2020. 128(3): p. 604-611.

CHAPTER 2: REVIEW OF LITERATURE

Human heat balance and its application in infant thermoregulation

The physiological goal of the human body is to maintain a steady-state core temperature, which necessitates heat balance, i.e., an equilibrium between the rate of internal heat production and net heat loss from the skin to the surrounding environment. Throughout the lifespan, the human body generates endogenous heat (metabolic heat generation from skeletal muscles and other organs) and must lose heat to maintain the body's core temperature which normally rests at a normothermic level of $\sim 37^{\circ}\text{C}$ [1]. During heat exposure, vasodilation of blood vessels occur and skin blood flow increases, allowing heat to be diverted from the body core to the skin, which increases skin temperature and heat loss to the environment [1]. Heat storage will occur in the human body if the rate of heat production exceeds the rate of heat loss, indicated by a rise in core temperature. Conversely, negative heat storage occurs and core temperature decreases when the rate of heat loss exceeds the rate of heat production, leading to hypothermia [2]. The primary defense against this is a vasoconstriction of the blood vessels of the skin followed by an increase in endogenous heat production through shivering thermogenesis. The human heat balance equation describes this dynamic equilibrium between heat production and heat loss as:

$$M - W = \pm C \pm K \pm R + E \pm S \quad (W)$$

In the above equation, M stands for metabolic energy expenditure, W for external work performed, C for convective heat transfer, K for conductive heat transfer, R for radiative heat transfer, E for evaporative heat loss from the skin surface, and S for net heat storage in the body. The left side of this equation represents heat production (H_{prod}) and the right side represents net heat loss. If this equation is balanced, heat storage is zero [2]. H_{prod} is quantified by calculating the rate of energy production (i.e., metabolic energy expenditure) and removing the proportion of that energy that is being utilised to perform work (i.e., external work performed). Metabolic rate (M) is derived by the following equation:

$$M = VO_2 \times \frac{\left\{ \left[\left(\frac{RER-0.7}{0.3} \right) \cdot 21.13 \right] + \left[\left(\frac{1.0-RER}{0.3} \right) \cdot 19.63 \right] \right\}}{60} \times 1000 \quad (W)$$

where VO_2 is the rate of oxygen consumed ($L \cdot min^{-1}$ STPD) and RER is the ratio of carbon dioxide produced and oxygen consumed, otherwise known as the respiratory exchange ratio. With every litre of oxygen consumed carbohydrates and fats yield 21.13kJ and 19.63kJ of energy, respectively [3]. The majority of human activities are inefficient, which means that they generally use less than 20% of an individual energy expenditure [2]. As a result, more than 80% of this energy is released as heat, which must then be transported from the body to the environment outside to avoid heat storage [2]. Since no external work is being done while at rest, it can be inferred that metabolic rate equates to heat production in infants under most circumstances, as the population of interest in this thesis [4].

Dry heat transfer

'Dry' or 'sensible' heat transfer is defined as the combination of convection, conduction, and radiation [1]. This is reflected on the right-hand side of the human heat balance equation. Convective heat transfer occurs as air moves over the skin's surface into the surrounding air [1]. The main factor determining convective rate and direction is the difference between skin and ambient temperature [1]. The first law of thermodynamics states that heat always moves along a temperature gradient from higher to lower temperatures. Therefore, in hotter conditions when ambient temperature exceeds skin temperature, this results in convective heat gain [1]. If ambient temperature is less than skin temperature, heat will then be lost by convection [1]. According to this concept, increasing airflow will intensify heat exchange, therefore adding more airflow, along with ambient temperatures above or below skin temperature would enhance convective heat gain or loss [1]. Using an example in the neonatal setting, a newborn when being carried through a cool

environment, such as the delivery room after birth, will lose heat to the air via convection [5].

Conduction is the process of transferring heat through skin surface contact with another solid object, and it can lead to both heat gain and heat loss. The magnitude of the temperature differential between the skin and the contacted solid surface, the amount of skin in contact with the material, and the substance's thermal conductivity all affect the amount of conductive heat transfer [1]. Conductive heat transfer may be calculated via the following equation:

$$K = -k \times (\Delta T / \Delta x) \times S \quad (W)$$

wherein k is the thermal conductivity of the material in contact with the skin ($W \cdot m^{-1} \cdot ^\circ C^{-1}$), ΔT is the temperature gradient ($^\circ C$), Δx is the thickness of the material heat is conducted through (m), and S is the surface area in contact with the conductive material (m^2) [6]. Conduction as a heat transfer process is typically minimal, however in a clinical scenario such as a newborn infant being laid onto a cold weighing scale in a delivery room, this heat exchange can be substantial. This is due to the heat that is exchanged between the infant's skin surface and the weighing scale that is colder, resulting in heat loss from the body. Conversely, if the surface of the weighing scale is warmer than that of the infant's skin surface, there will be heat gain from the weighing scale to the infant.

Radiation, the third avenue of heat exchange, refers to heat transfer by electromagnetic waves. Radiative heat sources can be ecologically derived, e.g., solar radiation, or man-made e.g., radiant heat lamp in an infant radiant warmer used in a hospital setting [7]. Following these examples, any material objects may absorb and produce electromagnetic waves at any temperature [8]. It is important to note that not all materials will heat up at the same rate or in the same way overall. One aspect that affects a material's capacity to both absorb and emit heat radiation is its emissivity, which is determined by the total amount of absorbed thermal radiation attainable by a

material, which is then divided by the energy emitted by the surface measured [8]. Although emissivity can aid in determining a material's radiative heat gain, the size of the material, the angle of exposure, and the amount of surface area that is exposed to thermal radiation plays a role in determining the maximum heat gain that can be achieved [1]. In radiative heat exchange, the temperature differential between the infant skin and the radiating body determines how quickly heat is lost. For instance, heat can be transmitted from the infant's body to a nearby, cooler wall. Alternately, heat from a radiant warmer lamp will be absorbed into the infant skin [5, 9].

Evaporative heat transfer

The most efficient way to dissipate heat is by evaporative or "insensible" heat loss, which releases 2426 joules of heat energy from the skin's surface for every gram of sweat that evaporates [10]. Sweat evaporation is the sole pathway in the heat balance equation through which only heat loss, not exchange, happens because it depends on the phase transition of sweat from liquid to vapour, which cannot be reversed [10]. The rate of evaporation is influenced by the difference in vapour pressure between the surface of the skin and the environment around it. When this difference is greater, as it is in dry conditions, evaporation occurs more quickly. Additionally, sweat evaporation is facilitated by air flow across the skin surface, therefore an increase in wind speed often results in an increase in evaporative heat loss provided moisture is present on the skin surface [1]. Evaporative heat loss at the skin surface is derived by the following equation:

$$E = h_e(p_1 - p_2) \quad (\text{W} \cdot \text{m}^2 \cdot \text{kPa})$$

where: E – rate of evaporative heat loss per unit area; h_e – evaporative heat transfer coefficient ($\text{W} \cdot \text{m}^2 \cdot \text{kPa}$); p_1 – skin surface water vapour partial pressure; p_2 – ambient air water vapour partial pressure.

Therefore, the amount of water vapour in the surrounding air, or humidity, has a significant impact on how quickly sweat can evaporate. For instance, in hot, dry environments with low environmental humidity, sweat secretions evaporate quickly, whereas in high humidity or tropical environments, sweat evaporation is limited because the air is already heavily saturated with water vapour.

At birth, evaporative heat loss occurs when liquid from wet skin, i.e., amniotic fluid, evaporates into the air around it when the wet newborn transitions from the uterus's perpetually warm environment to the birthing room's cooler, dryer environment. [11, 12]. The risks from excessive evaporative heat loss for a premature infant are dependent on three factors: the infant's postpartum moisture level, the skin's immaturity and water permeability, and the length of time the infant is exposed to drying agents such radiant warmers [13-15]. Therefore, these factors need to be considered to mitigate heat loss and maximise clinical outcomes when the newborn is adapting to the new external environment.

Based on the heat transfer avenues discussed, if no action is taken immediately after birth, a neonate's core and skin temperatures could decrease at a rate of approximately 0.1°C and 0.3°C per minute, respectively [16, 17]. A core body temperature of 36.4 to 36°C is considered mild hypothermia, 35.9°C to 32°C is considered moderate hypothermia, and less than 32°C is considered severe hypothermia, according to the World Health Organisation [11]. Therefore, at rest, a neutral thermal environment encourages a steady body temperature. The neutral thermal environment for infants had been previously described as the ambient temperature at which the preterm infant's body temperature is between 36.7°C and 37.3°C at rest, with core and skin temperature variations of less than 0.2° to 0.3°C/hour [5, 18]. Therefore, ideally, in a neutral thermal environment, heat loss or gain by dry and evaporative heat transfer would be low,

promoting infant thermal stability.

Neonatal skin and thermoregulation

Skin is a complex tissue organ and its existence is vital to thermoregulatory function in the human body [19]. Also known as the integumentary system, skin, from the top layer to bottom, consists of the epidermis, dermis and hypodermis. These layers conceptualise the outer ‘shell’ layer of the body, acting as a protective boundary layer for the bodily tissues from the external environment, thus maintaining homeostasis [20, 21]. This protective layer augments body temperature through conductive, convective, radiative, and evaporative mechanisms, all of which are controlled centrally via the central nervous system and effected peripherally via dermal vasculature and sweat glands [20, 22].

Neonatal skin physiology is notably different from adult skin. The stratum corneum, which is the most superficial skin layer that resides on the epidermis, acts as a protective epidermal barrier to prevent transepidermal water loss and penetration by external agents [23]. Transepidermal water loss is a form of insensible water loss from the skin via continuous diffusion of water through the epidermis and some secretion of sweat from immature infant sweat glands [24, 25]. As the structural integrity of the stratum corneum is related to gestational age at birth, this topmost skin layer is substantially thinner in infants born preterm (between 23 to less than 37 weeks of gestation) as it has not been fully formed yet, when compared to full term infants or adults [19, 23] leading to higher water loss. The rate of transepidermal water loss in an infant born at 29 weeks of gestation was determined to be $17 \text{ g/m}^2/\text{h}$, compared to an infant born full-term, which is at $4\text{--}8 \text{ g/m}^2/\text{h}$. This rate was demonstrated to be equal or lower than adults, indicating an effective water-loss skin barrier in full term infants, but not those born prematurely [26, 27]. It was also shown that infants in the subsequent months of life still exhibited higher levels of water loss compared to adults, and

stratum corneum development and maturity only appears adult-like after the first year of life [28].

Thus, infants, especially those born premature, have a less than ideal epidermal barrier. These high levels of insensible water loss transepidermally and resulting evaporative cooling from the infant skin surface compromises the ability of neonates and young infants to maintain normothermia [29]. A drop in skin temperature between 36°C to 35°C activates heat production in the infant by peripheral vasoconstriction and initiates non-shivering thermogenesis via the sympathetic activation of brown adipose tissue [17, 30]. Brown adipose tissue constitutes approximately 1.4 percent of the body mass of newborns with a birthweight greater than 2 kilograms, and is prominent in nuchal subcutaneous tissue, around the kidneys, the mediastinum and intrascapular regions [31]. Despite neonates having a relative abundance of brown adipose tissue, heat gain by non-shivering thermogenesis is insignificant as this is limited by the infant's large surface area in relation to the mass of heat-producing tissues, and the lack of subcutaneous fat insulation [32]. These neonates also have a low capacity to produce metabolic heat via shivering, except in cases of severe hypothermia [33]. Infants also rely fully on timely adult intervention as they do not exhibit adult behavioural thermoregulatory responses such as moving towards or away from hot or cold stimuli, and removing or wearing clothes, which influences their ability to attain thermal equilibrium.

Infants typically have a surface area-to-mass ratio up to four times greater than a typical adult, [34]. For example, based on the formula by Du Bois and Du Bois (Du Bois & Du Bois, 1916) for calculating body surface area ($\text{body surface area}[\text{m}^2] = \text{weight}[\text{kg}]^{0.425} \times \text{height}[\text{cm}]^{0.725} \times 0.007184$), for a typical adult weighing 70kg with a height of 1.8metres, his body surface area equals to 1.88m². His body surface area to mass ratio will then be 1.88m²/70kg = 0.027. The infants in our experimental studies, with a mean body weight of 2.12kg and a mean body length of 43.3cm

will equate to a body surface area of 0.15m^2 . The body surface area to mass ratio will then be $0.15\text{m}^2/2.12\text{kg} = 0.07$. From this example, the infants' body surface area to mass ratio in our studies is 2.6 times more than the typical adult. Coupled with limited vasomotor activity and lack of subcutaneous fat insulation, infants are thus more susceptible to significant evaporative heat loss, leading to hypothermia [30, 34, 35].

From a dry heat exchange perspective, this is a bidirectional issue depending on the ambient temperature. When ambient temperature is lower than skin temperature, a high body surface area to mass ratio can increase the rate of dry heat loss from the body (relative to mass) to the environment, potentially increasing the risk of hypothermia. This is potentially an issue as these newborns are in delivery suites, neonatal intensive care units or nurseries, which are typically air-conditioned. This lends itself to the need for devices such as radiant warmers to mitigate cold stress. When the ambient temperature is greater than the skin temperature, the high body surface area to mass ratio can have the reverse effect, making newborns more susceptible to dry heat uptake when heat energy flows down the temperature gradient from high to low. This poses an issue when infants are exposed to hot outdoor environments, such as whilst being transported in a stroller on a hot summer day, hence the need to mitigate this potential heat stress.

Radiant warmers in the clinical setting

As discussed in the preceding sections, infants, particularly those who are born preterm (births occurring between the 22nd and the 37th week of gestation) and with low birth weights (newborns with a birth weight of less than 2500 g), have a reduced ability to produce metabolic heat. When combined with a high surface area to volume ratio and an immature epidermal barrier, significant evaporative heat losses are observed [36]. As a result, low birth weight newborns are

more prone to cold stress, leading to hypothermia if their core body temperature is not maintained [36, 37]. Cold stress is also associated with lethargy, hypoglycaemia, low muscle tone, poor feeding, weight loss, vomiting, restlessness, pallor, and respiratory distress in these vulnerable infants, impacting on their growth and development leading to negative clinical outcomes [15, 38-41]. In light of this, maintaining a thermoneutral environment for the most vulnerable neonates born preterm and with very low birthweights is now standard practice in neonatal wards [42].

There has been some discussion over the best way to avoid heat loss in this vulnerable infant population. Control of the convective environment and the regulation of control of radiant losses are the two main strategies of thermal management. Radiant warmers are an example of the latter, whereby the infant is heated by a radiant heat source that is positioned horizontally overhead whilst lying in an open cot surrounded by low plexiglass walls, as seen in Figure 1 [32, 43]. These devices are controlled by narrow band proportional controllers, which detect small deviations from a temperature set point e.g., 36.0°C [44], and increase the radiant heat output if the infant is deemed below the set-point and reduce the radiant heat output if the infant is above the set-point. As such, an infant who would otherwise be exposed to the cold setting of an air-conditioned neonatal critical care unit is warmed by these devices' radiant heater [45]. Radiant heat transfer is advantageous in radiant warmers, as they reduce radiant heat loss and reverse it to net gain instead [32]. These warmers seek to deliver residual radiant heat such that the rate of net heat transfer from the infant to the surrounding environment via dry and evaporative heat transfer avenues balances the rate of metabolic heat production, resulting in a stable internal body temperature. Thus, the use of the radiant warmers to help regulate infant core temperature will be a primary focus of this thesis.

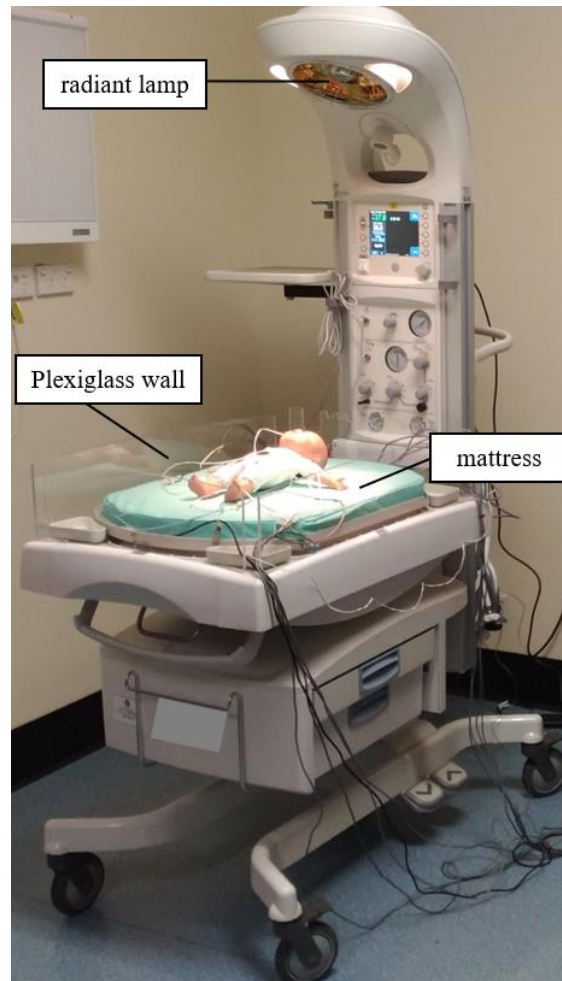


Figure 1: *Radiant warmer set up. The doll is placed in the centre of the mattress, to replicate an infant nursed under the radiant warmer.*

Whilst the use of the open radiant warmer promotes visibility and accessibility for nursing and medical staff in the treatment of preterm and unwell babies, greater transepidermal water loss and probable increases in metabolic rate occur when compared to the enclosed convective incubator, in which air temperature and humidity can be controlled [36]. While incubators are more adaptable and may be regulated using input from the skin, the air, or a combination of control factors, radiant warmers must always be servocontrolled to the skin temperature [42]. This means that when an infant is kept warm using a radiant warmer the amount of heat provided is controlled by a single local skin temperature sensor placed either on the anterior portion of the abdominal

wall or under the arm pit along the mid-axillary line of the thorax (T_{feedback}) [11, 46-48]. This system employed to regulate the intensity of radiant heat output from these warmers is therefore critical since too much or too little heat delivery can rapidly evolve into neonatal hyperthermia and hypothermia, respectively [11]. A Cochrane review determined that when compared to warming the air in the incubator to a set temperature, servocontrolling at skin temperature of 36°C, or near the thermoneutral point, reduces the neonatal death rate among low birth weight infants by nearly 30%, and even more so among infants with very low birth weights (birth weight of less than 1500 g) [49]. However, recent studies have also shown that this temperature measurement technique does not accurately reflect the deep (core) temperature of the infant and has led to transient, cyclical bouts of heat debt and heat storage and consequent fluctuations in deep core temperature and infant physiological strain [50]; and has the potential to lead to accidental bouts of overheating [51]. Moreover, large variations in local skin temperatures (e.g., chest, feet) have been observed despite the tight regulation of T_{feedback} , and a poor agreement between T_{feedback} and deep core temperature measured via rectal thermometry [52].

A point for consideration is the use of the abdominal or mid axillary line region as skin temperature sites, acting as a surrogate for infant core body temperature. These sites were suggested previously as they were accessible when the infant is in the supine position [32]. In the prone position, the ideal site is not established, however it was suggested that the skin over the scapular region was to be avoided, due to its abundance of brown adipose tissue [30]. Thus, it can be concluded that the site along the mid-axillary line was seen as a compromise, to optimise access regardless of infant position. However, given the considerations previously discussed, it is crucial that the measurement of infant core temperature, both directly measured and estimated, is accurate to ensure the appropriate external thermal management may be provided.

Measuring core body temperature

Despite it being a straightforward concept, there is little consensus regarding the temperature measurement that actually represents the body “core”. The core measurement sites advocated as a “gold standard” include the rectum [53], tympanic membrane [54, 55], nasopharynx [56], lower third of the oesophagus [57], pulmonary artery [58] and the bladder [59]. It is important to recognize however, that the temperature at each of these sites essentially represents that of the local tissue and as such differ, often greatly [60] depending upon tissue mass, blood supply, relative distance apart and proximity to other highly vascularized area or other factors altering local temperature. The physiological and practical significance of each “core” temperature measurement therefore varies.

It is logical however for health professionals to be primarily concerned with two particular temperatures: firstly, brain (or specifically the hypothalamus) temperature, since this is the location of the regulatory centre integrating thermal input from locations across the body [61] and is also highly sensitive to changes in local temperature of the brain itself [62]; and secondly, mixed blood temperature, since this most closely reflects the level of heat debt across the entire body [63]. By their very nature both of these measurements are highly invasive. Brain temperature cannot be directly measured in humans therefore alternative measures must be used. Tympanic membrane temperature was widely thought for a long time to be an accurate surrogate for brain temperature by virtue of a common blood supply with the same vasculature as the hypothalamus via the internal carotid artery [64]. However, this has since been disputed as the tympanic membrane is actually supplied by the external carotid artery and as such is easily contaminated by external factors [65]. However, it is still considered a “gold-standard” among many physicians [54, 55]. Nasopharyngeal temperature measured with a probe positioned in the nasopharynx and anatomically closest to the

brain has been shown to closely reflect epidural brain temperature in infants [56]. However, probe placement relative to the soft palate is crucial for accuracy and the probe must also be placed in an endotracheal tube to ensure that the passage of inspired and expired gases does not artificially alter the measurement.

It is widely considered that measuring mixed blood temperature is most accurately achieved by placing a probe directly into the pulmonary artery [58], but this is clearly very invasive and steeped with risks. Distal oesophageal temperature has been shown to precisely represent mixed blood temperature in adults during steady-state and transient conditions. Some have suggested that distal oesophageal temperature is less accurate in infants and children due to the minimal insulation between the tracheobronchial tree and the oesophagus, and the subsequent influence of inspired gases temperature [60]; however, this influence is commonly believed to be minimal. Bladder temperature precisely reflects pulmonary artery temperature in patients with a relatively high urine flow [66] and is therefore a suitable analogue but not much less invasive. The most practical site for clinically measuring deep body temperature is in the rectum which correlates well with pulmonary artery temperature during a steady-state and is widely employed as a reliable index of heat debt [67]. However, it was determined that rectal temperature lags significantly during temperature transients due to the insulative properties of the tissues surrounding this area [68] and measurements can be further influenced by the presence of an impacted stool [69].

All of the temperature measurements discussed present varying degrees of risk for discomfort, emotional upset and traumatic injury during insertion [54]; and in some cases, infants may have congenital malformations that do not allow the placement of a particular core temperature probe (e.g., rectal) [70]. A need therefore exists for a sufficiently accurate form of thermometry that is non-invasive. The traditional approach is to measure axillary temperature.

Advantages include that it is safe and easily accessible, and when measured directly over the artery can reflect deep body temperature [71]. However, in patients with a low cardiac output or marked peripheral vasoconstriction, axillary temperature does not correlate well with deeper core temperature measurements [58]. From a practical viewpoint, the measurement is also time-consuming, as it can take up to 11 minutes to attain a stable reading with an in-glass thermometer and 40 to 80 seconds with a digital thermometer [72].

Non-invasive methods for estimating core temperature

One non-invasive option for estimating core temperature uses a transcutaneous temperature sensor placed on the skin surface, often on the upper abdomen, as previously discussed [32,42]. This provides a continuous real-time measurement presenting a near-zero health risk. However, this is essentially a measurement of skin temperature and is therefore considerably lower than core temperature [73]. When used, common general practice employs a generic “correction factor” of +1°C in order to estimate true core temperature, but most corrective factors for any surrogate measure of core temperature have limited empirical grounding [73]. It is known that temperature gradients exist throughout the tissues of the body with the most pronounced being between the skin surface and core internal organs. In adults, this gradient can be several degrees Celsius, but in infants/neonates it is thought to be less pronounced due to low levels of cutaneous and tissue insulation [74]. It is therefore possible that a transcutaneous temperature probe may be a viable non-invasive surrogate measure for core temperature in this population.

Another method for consideration as a non-invasive surrogate measure for core temperature in the infant population is zero heat flux thermometry. The zero heat flux method of estimating deep core temperature is based on the assumption that if heat loss from the body's skin

surface is reduced to zero with appropriate thermal insulation on the skin, the gradient between deep core temperature and skin surface temperature will shift towards zero [75, 76]. The skin's surface temperature will then equalise with its deep core temperature [77].

The use of specialised zero-heat-flux thermometers involves placing a thermal insulator next to the skin (typically on the forehead region), which is covered by an electric heater. This heater is servocontrolled to remove heat transfer through the insulator, at which point the temperatures of the heater and the skin are equal [78, 79]. These thermometers can measure the temperature of tissues up to a centimetre below the skin's surface, which was shown to be adequate for estimating core temperature [80]. The benefits with this method include its non-invasive nature, ease of use and the potential in continuous monitoring temperature over a sustained period of time with minimal patient discomfort [78]. Furthermore, due to the effects of the insulation, the accuracy of the zero-heat-flux measurements is not influenced by ambient temperature [78]. The drawback is that it may take up to 15 minutes to achieve the final equilibrium temperature within 0.1°C, and this is dependent on the skin site location too [77]. However, this delay time is being mitigated with improving technology [81].

However, due to the specialised nature of these insulated thermistors, the zero heat flux thermometers are costly for daily use and are typically used in specialised clinical settings only, e.g. operating theatres [77]. Several studies have been conducted to evaluate the use of the zero heat flux approach in intensive care and surgical settings and have determined that these specialised zero heat flux thermometers are adequate in substituting invasive thermometry methods either via the distal oesophagus, pulmonary artery or iliac artery [78, 81, 82]. However, the patients in these studies were either sedated, or had undergone regional anaesthesia. In a non-surgical setting, Teunissen et. al applied the zero heat flux thermometry technique on exercising

(cycle ergometer) adult individuals in hot ambient conditions and determined that the zero heat flux method provided a reliable estimation of oesophageal temperature with little to no time delay [83]. However, as this study utilised a prototype sensor, its accessibility to the wider population remains to be determined.

Conceptually, zero heat flux may also be achieved by different means of insulation, without needing a specialised heater on the skin, as long as heat loss from the skin is reduced to zero. This can potentially be achieved by covering a standard skin temperature probe with a suitable insulatory material, or direct contact of the skin surface onto an insulating material e.g., mattress [84, 85]. Based on this understanding, the zero-heat flux approach can be deemed as a viable method in the infant population, as the gradient between infant skin and the internal organs is already reduced, due to the smaller body tissue depth and lack of subcutaneous fat, compared to adults [74], as previously discussed. Studies by Dollberg et al and van der Spek et al [84, 85] demonstrated the efficacy of this technique, however they investigated infants who were nursed in incubators, instead of servocontrolled radiant warmers, which is the device of interest in this thesis. The infants studied were also in the extremely low birth weight (<1000 g) and very low birth weight (<1500 g) categories, inferring to the lack of skin layer depth which lessens the gradient between skin and internal organs, which facilitates the zero-heat flux method. However, it is unclear if similar findings can be established in slightly larger and older infants nursed under radiant warmers in the neonatal intensive care unit setting. Blackburn et. al adopted the zero-heat flux approach in infants using a standard thermocouple temperature probe placed on the abdomen, back and axilla [86]. They determined that the abdomen and back skin sites, when in contact with the mattress surface over a one-hour period, were in agreement with the axillary skin site measurements in lieu of the insulatory effect. However, these comparisons were made based off

thermocouple readings from another skin site (situated in the deep axilla region) as an inference to core temperature, instead of using established methods of measuring core temperature e.g., rectal thermometry. It is thus unclear if these contact site temperature measurements are in true agreement with core body temperature, and if these findings are applicable over a longer duration of nursing care.

Stroller usage and its considerations in usage in hot weather conditions

Another ecologically valid setting in which infants will experience heat stress is the outdoors during hot weather. Every year, millions of babies are born across the globe. Extracting figures from 2021 to 2023, some examples from the Northern Hemisphere include the European Union registering more than 4.09 million births [87] and the United States of America tallying 3.66 million births [88]. In the Southern Hemisphere, Niger registered the highest birth rate of 44.22 births per 1000 people in its population, totaling more than 1 million births [89]; and Australia reporting 320,900 births [90]. In recent years, with the rise in summer heatwaves, these same parts of the world also clocked up unprecedented highest recorded temperatures. Outdoor ambient temperatures reached as high as 47°C in Portugal in Europe [91] and 50.7°C in Western Australia on the afternoon of 13 January 2022 [92]. Such heat extremes pose serious health risks leading to high infant mortality rates and heat related hazards in infants and children [93, 94], although such risks can be mitigated through the implementation of evidence-based risk management actions [94] which this thesis aims to address.

Keeping in mind the importance of maternal well-being after delivery, outdoor physical activity is also encouraged for the mother postpartum. This is not only to boost their physical activity levels postpartum and improve the level of overall maternal fitness [95], but to also allow

opportunities for bonding between mother and child, facilitate socialisation, improve mental well-being and reduce postnatal stress and depression [96]. As such, brisk walking and jogging with the infants and strollers in tow are typical scenarios of combining both aspects of outdoor exercise and maternal/infant bonding [97], and this should be encouraged for all seasons, including hot summer weather when carried out judiciously, without compromising the safety of both the mother and the infant [98, 99].

Conventional advice recommends avoiding stroller use during the hottest part of the day when solar radiation intensity is at its peak, often between midday and 3pm [100]. Albeit well-intended, this advice may not be practical given the day to day needs of parents and caregivers and their infants in which outdoor heat exposure may be unavoidable, such as running errands or as a means of transportation to a specific location over long distances [97], which at times, cannot be dictated by the time of day. Therefore, there is a need to investigate stroller cooling interventions to help mitigate the negative impacts of stroller heat stress exposure during times when outdoor heat exposure cannot be avoided altogether.

Various cooling interventions have been shown to be efficacious in reducing heat stress in adult populations. These include electric and misting fan usage, self-dousing, cold-water ingestion, ice towel application, activity reduction and clothing optimisation and removal [101]. Whilst some of these strategies may be feasible for use with infants, there are several considerations unique to this population which may limit the utility these cooling interventions. For example, infants have a surface area-to-mass ratio approximately four times higher than adults, which may result in excessive cooling when certain interventions are applied (e.g., ice-towel application) and result in inadvertent bouts of cold stress and discomfort, resulting in infant irritability. Additionally, infants are also unable to behaviourally thermoregulate independently and, therefore, strategies such as

cold-water ingestion, activity reduction and clothing optimisation will require active intervention by the caregiver. Finally, any potential cooling intervention introduced must be viable within the confines of the stroller carriage without causing disruption to the infant.

Nevertheless, some methods to cool infants placed in strollers in hot weather have been adopted by parents and caregivers and are often promoted in public-facing recommendations. Low-cost strategies such as the use of cloth coverings e.g. muslin, flannelette and thin cotton blankets attempt to block out the radiant heat from the sun [102-104] and minimise exposure to the harmful effects of ultraviolet radiation [105], which increases the risk of skin melanoma in later life [106]. However, overzealous attempts in covering up the strollers to minimise harmful sun exposure, especially with the use of heavy blankets may impede air ventilation. Other reasons parents drape cloth coverings over stroller carriages are to reduce visual stimuli to encourage infants to sleep, reduce unwanted attention from strangers and limit the infants' exposure to cigarette smoke and other air pollutants [103, 107]. Discussions regarding air quality surrounding the infants in strollers and the potential risk of sudden infant death syndrome (SIDS) has also been raised in previous literature [104]. However, concerns surrounding thermal strain within this same environment remains unsubstantiated by research, emphasising a gap in the literature.

Another potential stroller cooling method is the use of a portable battery-operated clip-on fan, which increases the circulation of air within the stroller carriage [108]. This strategy is considered convenient as the portable battery-operated clip-on fan is affordable and readily available, although its efficacy in reducing the stroller carriage temperature, and in turn attenuating the heat stress experienced by infants, remains to be determined. Other strategies to mitigate the heat within stroller carriages include the use of specialised parasols and sunshades [109] although this may come with a higher financial cost and thus may not be the primary option for some

parents.

Even though the use of the abovementioned strategies is reported in the media, parenting websites and observed in day-to-day parenting [100, 102], interestingly, there is a paucity in peer-reviewed evidence to support these suggested interventions. For example, there is debate regarding the use of coverings, regardless of its material and thickness, as these may further trap heat within the confined, enclosed space of the stroller carriage [102-104, 110, 111], even when draped in a single layer [112], subjecting the infants within to risk of overheating. Articles highlighting this practice as being potential fatal have also been in circulation in the media [102, 113, 114], however the potential risk is often inferred from literature addressing infant fatalities in enclosed vehicles (i.e. cars) during hot weather [115-118] and may not accurately reflect the heat-stress risk in the context of strollers. Further research is therefore warranted to further examine the issue of stroller heat stress and to identify solutions to help mitigate the associated heat-related risk.

Likewise, the use of the portable clip-on fan may inadvertently circulate hot air within the carriage especially during use in hot and dry weather [119]. Drawing on current research in electric fan use for the adult population, Morris et. al determined that electric fans can provide effective cooling in a hot and humid environment where ambient temperature reached 40°C with 50% relative humidity but were detrimental in very hot and dry conditions where ambient temperature reached 47°C with 10% relative humidity [120]. Foster et. al also highlighted that when ambient temperature is ≥ 40 °C, electric fans are deemed ineffective and potentially harmful when relative humidity is below 50% [121]. Thus, depending on environmental conditions, convective and evaporative heat transfer avenues may be significantly impacted by increased air movement, whether brought on by purposeful electric fan use or by natural wind currents [121]. These findings thus need to be taken into consideration when applying the use of a clip-on fan in a stroller, and

its effect on the infant population, which have yet to be determined.

Conversely, when applying the principles of evaporative cooling [122], it can be considered that moistening cloth coverings that are light and absorbent, such as muslin, may assist in keeping the stroller carriage cool. This concept can be inferred from recent studies involving adult participants in which wearing water-soaked attire in hot and moderately humid to humid conditions mitigated the rise in core body temperature and alleviate heat strain via evaporative cooling over a large surface area [123, 124]. This wet clothing method will not be sensible with young infants, however, the effects of evaporative cooling may be harnessed in different ways to keep the stroller cool. For example, draping a wet cloth covering over the stroller canopy may be an effective way of extracting heat from the stroller via evaporative pathways. The efficacy of this method in an ecologically valid setting e.g., draping a moistened cloth over a stroller in hot, humid weather remains to be established.

Based on the above, there is evidence to support fan use and the efficacy of evaporative cooling on moistened clothing in adults. However, there is a paucity in empirical literature that systematically investigates the efficacy of these cooling strategies in infant strollers. Deriving clear guidelines in health and public policy in heat stress management will assist parents in reducing financial stress and improve health equity [125]. Thus, the availability of such evidence is necessary to shape parents' and caregivers' decision-making processes in maximising infant comfort in hot weather.

Conclusion

Infants, especially if born prematurely and of a low birth weight, are a vulnerable population in the domain of thermoregulation, regardless of settings. Exposure to extreme heat or cold stress can lead to physiological strain and undesirable health outcomes. Therefore, maintaining normothermia is critical to protect the infant. The overall purpose of this thesis is two-fold – firstly, to evaluate potential methods of non-invasive temperature monitoring that can accurately reflect core thermometry in infants nursed under radiant warmers in an intensive care setting; and secondly, to determine interventions to cool a stroller in hot, outdoor environments. To address certain gaps in the research literature, this thesis will focus on:

- a) measuring skin temperature over the carotid artery site as a non-invasive method to serve as a surrogate to core body temperature measured invasively. Although this method has been determined to be effective in sedated children under general anaesthesia in an operating theatre, its efficacy has yet to be determined in premature and term infants nursed under a radiant warmer in the NICU setting.
- b) using skin sites as contact points in investigating the efficacy of zero heat flux thermometry. This has been researched in premature infants nursed in enclosed incubators for short durations, but yet to be determined for premature and term infants nursed in open care radiant warmers over a continuous period in the NICU setting.
- c) determining the efficacy of fan use and employing evaporative cooling methods, which has been shown to be effective in cooling the adult population in hot and humid conditions, but yet to be investigated in cooling a stroller in hot weather.

Literature Review References

1. Parsons, K.C., *Human Thermal Environments : The Effects of Hot, Moderate, and Cold Environments on Human Health, Comfort, and Performance, Third Edition*. 3rd ed. ed. EBL. 2015, Hoboken: CRC Press.
2. Kenny, G.P. and O. Jay, *Thermometry, Calorimetry, and Mean Body Temperature during Heat Stress*. *Comprehensive Physiology*, 2013. **3**(4): p. 1689-1719.
3. Gagge, A.P. and Y. Nishi, *Heat Exchange Between Human Skin Surface and Thermal Environment*. 2010, John Wiley & Sons, Inc: Hoboken, NJ, USA. p. 69-92.
4. Snellen, J.W., *External work in level and grade walking on a motor-driven treadmill*. *Journal of Applied Physiology*, 1960. **15**(5): p. 759-763.
5. Knobel, R.B., *Fetal and Neonatal Thermal Physiology*. *Newborn and Infant Nursing Reviews*, 2014. **14**(2): p. 45-49.
6. Cramer, M.N. and O. Jay, *Biophysical aspects of human thermoregulation during heat stress*. *Autonomic Neuroscience*, 2016. **196**: p. 3-13.
7. Baumgart, S., *Radiant heat loss versus radiant heat gain in premature neonates under radiant warmers*. *Biology of the Neonate*, 1990. **57**(1): p. 10.
8. Mazumder, S. and F. Modest Michael, *Fundamentals of Thermal Radiation*, in *Radiative Heat Transfer*. 2022, Elsevier.
9. Çınar, N.D. and T.M. Filiz, *Neonatal thermoregulation*. *Journal of Neonatal Nursing*, 2006. **12**(2): p. 69-74.
10. Wenger, C.B., *Heat of evaporation of sweat: thermodynamic considerations*. *Journal of Applied Physiology*, 1972. **32**(4): p. 456-459.

11. WHO, *Thermal Protection of the Newborn: a practical guide*. 1997, World Health Organisation: Geneva.
12. Hammarlund, K., et al., *Transepidermal water loss in newborn infants: V. Evaporation from the skin and heat exchange during the first hours of life*. Acta Paediatrica, 1980. **69**(3): p. 385-392.
13. Ellis, J., *Neonatal hypothermia*. Journal of Neonatal Nursing, 2005. **11**(2): p. 76-82.
14. Chitty, H. and J. Wyllie, *Importance of maintaining the newly born temperature in the normal range from delivery to admission*. Seminars in Fetal Neonatal Medicine, 2013. **18**(6): p. 362-8.
15. Laptook, A.R. and M. Watkinson, *Temperature management in the delivery room*. Seminars in Fetal and Neonatal Medicine, 2008. **13**(6): p. 383-391.
16. Adamson, J.S.K. and M.E. Towell, *Thermal homeostasis in the fetus and newborn*. Anesthesiology (Philadelphia), 1965. **26**(4): p. 531-548.
17. Waldron, S. and R. MacKinnon, *Neonatal Thermoregulation*. Infant, 2007. **3**(3): p. 101-104.
18. Sauer, P.J., H.J. Dane, and H.K. Visser, *New standards for neutral thermal environment of healthy very low birthweight infants in week one of life*. Archives of Disease in Childhood, 1984. **59**(1): p. 18-22.
19. Mancini, A.J., *Skin*. Pediatrics, 2004. **113**(4): p. 1114-1119.
20. Parsons, K.C., *Human Thermal Environments*. 2003, London and New York: Taylor and Francis Group. 560.
21. Romanovsky, A.A., *Skin temperature: its role in thermoregulation*. Acta Physiologica, 2014. **210**(3): p. 498-507.

22. Hall, J.E., *Guyton and Hall Textbook of medical physiology*. 13th;Thirteenth;13; ed. 2016, Philadelphia, PA: Elsevier.
23. Visscher, M. and V. Narendran, *Neonatal Infant Skin: Development, Structure and Function*. Newborn and Infant Nursing Reviews, 2014. **14**(4): p. 135-141.
24. Sedin, G., et al., *Measurements of Transepidermal Water Loss on Newborn Infants*. Clinics in Perinatology, 1985. **12**(1): p. 79-99.
25. Bettley, F. and K.A. Grice, *A method for measuring the transepidermal water loss and a means of inactivating sweat glands*. British Journal of Dermatology 1965. **77**(12): p. 627-638.
26. Kelleher, M.M., et al., *Newborn Transepidermal Water Loss Values: A Reference Dataset*. Pediatric Dermatology, 2013. **30**(6): p. 712-716.
27. Raone, B., et al., *Transepidermal Water Loss in Newborns Within the First 24 Hours of Life: Baseline Values and Comparison with Adults*. Pediatric Dermatology, 2014. **31**(2): p. 191-195.
28. Nikolovski, J., et al., *Barrier Function and Water-Holding and Transport Properties of Infant Stratum Corneum Are Different from Adult and Continue to Develop through the First Year of Life*. Journal of Investigative Dermatology, 2008. **128**(7): p. 1728-1736.
29. Watkinson, M., *Temperature control of premature infants in the delivery room*. Clin Perinatol, 2006. **33**(1): p. 43-53, vi.
30. Aherne, W. and D. Hull, *Brown adipose tissue and heat production in the newborn infant*. Journal of Pathology and Bacteriology, 1966. **91**: p. 223-234.
31. Merklin, R.J., *Growth and distribution of human fetal brown fat*. The Anatomical record, 1974. **178**(3): p. 637-645.

32. Bell, E.F., *Infant incubators and radiant warmers*. Early Human Development, 1983. **8**(3): p. 351-375.
33. Székely, M. and J. Garai, *Thermoregulation and age*. Handbook of Clinical Neurology, 2018. **156**: p. 377-395.
34. Polin, R.A., *Fetal and neonatal physiology*. Sixth edition. ed. 2021, Philadelphia, Pennsylvania: Elsevier.
35. Du Bois, D. and Du Bois E.F, *A formula to estimate the approximate surface area if height and weight be known*. Archives of Internal Medicine, 1916. **17**:863-71
35. Rutter, N. and D. Hull, *Response of term babies to a warm environment*. Archives of Disease in Childhood, 1979. **54**(3): p. 178-183.
36. Narendran, V. and S.B. Hoath, *Thermal management of the low birth weight infant: A cornerstone of neonatology*. The Journal of Pediatrics, 1999. **134**(5): p. 529-531.
37. Mance, M.J., *Keeping infants warm: Challenges of hypothermia*. Advances in Neonatal Care, 2008. **8**(1): p. 6-12.
38. Hackman, P., *Recognizing and Understanding the Cold-Stressed Term Infant*. Neonatal Network, 2001. **20**(8): p. 35-41.
39. Gandy, G.M., et al., *Thermal environment and acid-based homeostasis in human infants during the first few hours of life*. The Journal of Clinical Investigation, 1964. **43**(4): p. 751-758.
40. Pomerance, J.J., C. Madore, and L. Gluck, *Effect of temperature on survival of infants with RDS*. Pediatric Research, 1974. **8**(4): p. 449-449.
41. Baumgart, S., *Iatrogenic hyperthermia and hypothermia in the neonate*. Clinics in Perinatology, 2008. **35**(1): p. 183-97, ix-x.

42. Flenady, V. and P.G. Woodgate, *Radiant warmers versus incubators for regulating body temperature in newborn infants (review)*. Cochrane Database of Systematic Reviews, 2009(2): p. 1-41.
43. Wheldon, A.E. and N. Rutter, *The heat balance of small babies nursed in incubators and under radiant warmers*. Early Human Development, 1982. **6**: p. 131-143.
44. GE, *PandaTM and GiraffeTM Warmers service manual*, G.E. Company, Editor. 2017: USA.
45. LeBlanc, M.H., *Thermoregulation: Incubators, Radiant Warmers, Artificial Skins, and Body Hoods*. Clinics in Perinatology, 1991. **18**(3): p. 403-422.
46. Hunter New England Local Health District, *Local Guidelines: Thermoregulation of the neonate in NICU*. 2015, New South Wales Health, Australia: John Hunter Children's Hospital.
47. The Children's Hospital at Westmead, *Thermoregulation in Neonatal Care*. 2021, Sydney Children's Hospital Network, Australia.
48. The Royal Children's Hospital Melbourne. *Assisted Thermoregulation*. Clinical Guidelines (Nursing) 2020; Available from: https://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Thermoregulation_in_the_Preterm_Infant/#management.
49. Sinclair, J.C. and J.C. Sinclair, *Servo-control for maintaining abdominal skin temperature at 36C in low birth weight infants*. Cochrane library, 2002. **2010**(1).
50. Molgat-Seon, Y., et al., *Assessing neonatal heat balance and physiological strain in newborn infants nursed under radiant warmers in intensive care with fentanyl sedation*. European Journal of Applied Physiology, 2014. **114**(12): p. 2539-49.

51. Molgat-Seon, Y., et al., *Accidental overheating of a newborn under an infant radiant warmer: a lesson for future use*. Journal of Perinatology, 2013. **33**(9): p. 738-9.
52. Chaseling, G.K., et al., *Body temperature mapping in critically ill newborn infants nursed under radiant warmers during intensive care*. Journal of Perinatology, 2016. **36**(7): p. 540-3.
53. Rotello, L.C., L. Crawford, and T.E. Terndrup, *Comparison of infrared ear thermometer derived and equilibrated rectal temperatures in estimating pulmonary artery temperatures*. Critical Care Medicine, 1996. **24**(9): p. 1501-1506.
54. El-Radhi, A.S. and W. Barry, *Thermometry in paediatric practice*. Archives of Disease in Childhood, 2006. **91**(4): p. 351-6.
55. El-Radhi, A.S. and S. Patel, *An evaluation of tympanic thermometry in a paediatric emergency department*. Emergency Medicine Journal, 2006. **23**(1): p. 40-1.
56. Ko, H.K., et al., *Methodological investigation of measuring nasopharyngeal temperature as noninvasive brain temperature analogue in the neonate*. Intensive Care Medicine, 2001. **27**(4): p. 736-42.
57. Stoen, R. and D.I. Sessler, *The thermoregulatory threshold is inversely proportional to isoflurane concentration*. Anesthesiology, 1990. **72**(5): p. 822-7.
58. Holtzclaw, B.J., *Monitoring body temperature*. AACN Clinical Issues in Critical Care Nursing, 1993. **4**(1): p. 44-55.
59. Erickson, R.S. and T.M. Woo, *Accuracy of infrared ear thermometry and traditional temperature methods in young children*. Heart Lung, 1994. **23**(3): p. 181-95.
60. Bissonnette, B., *Temperature monitoring in pediatric anesthesia*. International Anesthesiology Clinics, 1992. **30**(3): p. 63-76.

61. Parsons, K.C., *Human Thermal Environments*. 2nd ed. 2003, London: Taylor & Francis.
62. Hammel, H.T., et al., *Temperature Regulation By Hypothalamic Proportional Control With An Adjustable Set Point*. Journal of Applied Physiology, 1963. **18**: p. 1146-54.
63. Mekjavic, I.B. and M.E. Rempel, *Determination of esophageal probe insertion length based on standing and sitting height*. Journal of Applied Physiology, 1990. **69**(1): p. 376-9.
64. Leick-Rude, M.K. and L.F. Bloom, *A comparison of temperature-taking methods in neonates*. Neonatal Network, 1998. **17**(5): p. 21-37.
65. Neubeck, S. and R.D. Hansen, *Tympanic thermometers: how accurate?* Nursing 98 Australia [Suppl], 1998.
66. Horrow, J.C. and H. Rosenberg, *Does urinary catheter temperature reflect core temperature during cardiac surgery?* Anesthesiology, 1988. **69**(6): p. 986-9.
67. Bissonnette, B., D.I. Sessler, and P. LaFlamme, *Intraoperative temperature monitoring sites in infants and children and the effect of inspired gas warming on esophageal temperature*. Anesthesia & Analgesia, 1989. **69**(2): p. 192-6.
68. Maxton, F.J., L. Justin, and D. Gillies, *Estimating core temperature in infants and children after cardiac surgery: a comparison of six methods*. Journal of Advanced Nursing, 2004. **45**(2): p. 214-22.
69. Bernardo, L.M., R. Henker, and J. O'Connor, *Temperature measurement in pediatric trauma patients: A comparison of thermometry and measurement routes*. Journal of Emergency Nursing, 1999. **25**(4): p. 327-9.
70. Frank, J.D. and S. Brown, *Thermometers and rectal perforations in the neonate*. Archives of Disease in Childhood, 1978. **53**(10): p. 824-5.

71. O'Toole, S., *Temperature measurement devices*. Prof Nurse, 1998. **13**(11): p. 779-84, 786.
72. Jirapaet, V. and K. Jirapaet, *Comparisons of tympanic membrane, abdominal skin, axillary, and rectal temperature measurements in term and preterm neonates*. Nursing & Health Sciences, 2000. **2**(1): p. 1-8.
73. Sund-Levander, M., et al., *Errors in body temperature assessment related to individual variation, measuring technique and equipment*. International Journal of Nursing Practice, 2004. **10**(5): p. 216-23.
74. Hey, E.N. and G. Katz, *The Range of Thermal Insulation in the Tissues of the New Born Baby*. Journal of Physiology, 1970. **207**: p. 667-681.
75. Fox, R.H., et al., *A New Method for Monitoring Deep Body Temperature from the Skin Surface*. Clinical Science and Molecular Medicine, 1973. **44**(1): p. 81-86.
76. Togwa, T., et al., *A modified internal temperature measurement device*. Medical & Biological Engineering, 1976. **14**(3): p. 361-364.
77. Yamakage, M. and A. Namiki, *Deep temperature monitoring using a zero-heat-flow method*. Journal of Anesthesia, 2003. **17**: p. 108-115.
78. Eshraghi, Y., et al., *An Evaluation of a Zero-Heat-Flux Cutaneous Thermometer in Cardiac Surgical Patients*. Anesthesia and Analgesia, 2014. **119**: p. 543-9.
79. Sessler, D., *Temperature Monitoring and Perioperative Thermoregulation*. Anesthesiology (Philadelphia), 2008. **109**(2): p. 318-338.
80. Matsukawa, T., et al., *Comparison of distal oesophageal temperature with deep and tracheal temperatures*. Canadian Journal of Anesthesia, 1997. **44**(4): p. 433-438.
81. Kimberger, O., et al., *Accuracy and precision of a novel non-invasive core thermometer*. British Journal of Anaesthesia, 2009. **103**(2): p. 226-31.

82. Dahyot-Fizelier, C., et al., *Accuracy of Zero-Heat-Flux Cutaneous Temperature in Intensive Care Adults*. Critical Care Medicine, 2017. **45**: p. e715–e717.
83. Teunissen, L.P.J., et al., *Non-invasive continuous core temperature measurement by zero heat flux*. Physiological Measurement, 2011. **32**: p. 559-570.
84. Dollberg, S., et al., *Effect of insulated skin probes to increase skin-to-environmental temperature gradients of preterm infants cared for in convective incubators*. The Journal of Pediatrics, 1994. **124**(5): p. 799-801.
85. van der Spek, R.D., R.A. van Lingen, and D. van Zoeren-Grobbe, *Body temperature measurement in VLBW infants by continuous skin measurement is a good or even better alternative than continuous rectal measurement*. Acta Paediatrica, 2009. **98**(2): p. 282-5.
86. Blackburn, S., et al., *Neonatal thermal care, part III: The effect of infant position and temperature probe placement*. Neonatal Network 2001. **20**(3): p. 25-30.
87. Eurostat. *Fertility statistics*. 2023; Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Fertility_statistics.
88. CDC. *Centers for Disease Control and Prevention: Births and Natality*. 2023; Available from: <https://www.cdc.gov/nchs/fastats/births.htm>.
89. theglobaleconomy.com. *Birth rate - Country rankings*. 2023; Available from: https://www.theglobaleconomy.com/rankings/birth_rate/#:~:text=The%20average%20for%202021%20based,countries%20where%20data%20are%20available.
90. ABS. *Australian Bureau of Statistics: National, state and territory population*. 2022; Available from: <https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/latest-release>.

91. BBC. *BBC News. Climate change: Europe's warm summer shatters records.* 2022; Available from: <https://www.bbc.com/news/science-environment-62833937>.
92. Hannam, P. *Australia matches its hottest day on record as Western Australia town hits 50.7C.* 2022; Available from: <https://www.theguardian.com/australia-news/2022/jan/13/hottest-day-on-record-in-parts-of-western-australia-as-temperature-reaches-50c>.
93. Basaga, et al., *Heat Waves and Cause-specific Mortality at all Ages.* Epidemiology, 2011. **22**(6): p. 765-772.
94. Ebi, K.L., et al., *Hot weather and heat extremes: health risks.* The Lancet, 2021. **398**(10301): p. 698-708.
95. Inge, P., et al., *Exercise after pregnancy.* Australian Journal of General Practice, 2022. **51**(3): p. 117-121.
96. Currie, J.L. and E. Develin, *Stroll Your Way To Well-Being: A Survey Of The Perceived Benefits, Barriers, Community Support, And Stigma Associated With Pram Walking Groups Designed For New Mothers, Sydney, Australia.* Health Care for Women International, 2002. **23**(8): p. 882-893.
97. Birken, C.S., et al., *Parents' perception of stroller use in young children: a qualitative study.* BMC Public Health, 2015. **15**(808).
98. Brown, W.J., et al., *Australian guidelines for physical activity in pregnancy and postpartum.* Journal of Science and Medicine in Sport, 2022. **25**(6): p. 511-519.
99. Australia, S.M., *SMA Position Statement Exercise in Pregnancy and the Postpartum Period.* 2016: www.sma.org.au.

100. McKimmie, M. *Babies at risk from covered prams* 2012; Available from: health.thewest.com.au/news/115/babies-at-risk-from-covered-prams.
101. Jay, O., et al., *Reducing the health effects of hot weather and heat extremes: from personal cooling strategies to green cities*. The Lancet (British edition), 2021. **398**(10301): p. 709-724.
102. *The Local SE. Swedes risk infants' lives by covering up prams*. 2014; Available from: <https://www.thelocal.se/20140711/swedes-risk-infants-lives-by-covering-up-prams>.
103. Wilson, L., S. Quine, and M. Lewis, *Hiding under the blankets: reasons why parents cover infants' strollers and prams*. Neonatal, Paediatric, and Child Health Nursing, 2010. **13**(2): p. 13-17.
104. Wilson, L., *Discussion paper: The great pram cover-up-a cautionary tale*. Neonatal, Paediatric and Child Health Nursing, 2008. **11**(1): p. 26-28.
105. Moise, A.F., H.P. Gies, and S.L. Harrison, *Estimation of the annual solar UVR exposure dose of infants and small children in tropical Queensland, Australia*. Photochemistry and Photobiology, 1999. **69**(4): p. 457-63.
106. Dobbinson, S.P., et al., *Children's sun exposure and sun protection: Prevalence in Australia and related parental factors*. Journal of the American Academy of Dermatology, 2012. **66**(6): p. 938-947.
107. Chang, A.B., et al., *Altered arousal response in infants exposed to cigarette smoke*. Archives of Disease in Childhood, 2003. **88**(1): p. 30-33.
108. Slaton, J. *Best stroller fans*. 2023; Available from: https://www.babycenter.com/baby-products/strollers-and-travel-systems/best-stroller-fans_40009180.

109. National Health Service (NHS). *Keeping your baby safe in the sun*. 2021; Available from: <https://www.nhs.uk/conditions/baby/first-aid-and-safety/safety/safety-in-the-sun/>.
110. NSW Health. *Babies and children in the heat*. 2022; Available from: <https://www.health.nsw.gov.au/environment/beattheheat/Pages/babies-children-hot-weather.aspx>.
111. *The dangers of covering your pram*. 2022; Available from: <https://rednose.org.au/news/the-dangers-of-covering-your-pram>.
112. O'Callaghan, P.W. and S.D. Probert, *Thermal insulation provided by dry, single-layer clothing materials*. *Applied Energy*, 1976. 2(4): p. 269-277.
113. Christian, N. *Heatwave warning: Common pram habit could be potentially fatal for babies and young kids*. 2019; Available from: <https://thewest.com.au/lifestyle/parenting/heatwave-warning-common-pram-habit-could-be-potentially-fatal-for-babies-and-young-kids-ng-81b054ca62b17dd6cd7c6b651c14a6a9>.
114. Payton, M. *Parents placing a blanket over baby's pram in hot weather 'put their children at risk'*. 2016; Available from: <https://www.independent.co.uk/life-style/health-and-families/health-news/uk-heat-sun-pram-stroller-parents-blanket-over-baby-pram-in-hot-weather-put-their-children-at-risk-a7145311.html>.
115. Vanos, J.K., et al., *Evaluating the impact of solar radiation on pediatric heat balance within enclosed, hot vehicles*. *Temperature (Austin)*, 2018. 5(3): p. 276-292.
116. Grundstein, A., S. Duzinski, and J. Null, *Impact of dangerous microclimate conditions within an enclosed vehicle on pediatric thermoregulation*. *Theoretical and Applied Climatology*, 2015. 127(1-2): p. 103-110.

117. Grundstein, A.J., et al., *Evaluating infant core temperature response in a hot car using a heat balance model*. Forensic Science, Medicine and Pathology, 2015. **11**(1): p. 13-9.
118. McLaren, C., J. Null, and J. Quinn, *Heat stress from enclosed vehicles: moderate ambient temperatures cause significant temperature rise in enclosed vehicles*. Pediatrics, 2005. **116**(1): p. e109-12.
119. Jay, O., et al., *Should electric fans be used during a heat wave?* Applied Ergonomics, 2015. **46**: p. 137-143.
120. Morris, N.B., et al., *Electric fan use for cooling during hot weather: a biophysical modelling study*. The Lancet: Planetary Health, 2021. **5**(6): p. e368-e377.
121. Foster, J., et al., *Quantifying the impact of heat on human physical work capacity; part II: the observed interaction of air velocity with temperature, humidity, sweat rate, and clothing is not captured by most heat stress indices*. International Journal of Biometeorology, 2022. **66**(3): p. 507-520.
122. Li, X., et al., *Superabsorbent Fabric Based on Weft-Back Weave Structure for Efficient Evaporative Cooling*. Advanced Materials Interfaces, 2021. **8**(1): p. 2001329-n/a.
123. Song, W., F. Wang, and C. Zhang, *Intermittent wetting clothing as a cooling strategy for body heat strain alleviation of vulnerable populations during a severe heatwave incident*. Journal of Thermal Biology, 2019. **79**: p. 33-41.
124. Cramer, M.N., et al., *Keeping older individuals cool in hot and moderately humid conditions: wetted clothing with and without an electric fan*. Journal of Applied Physiology 2020. **128**(3): p. 604-611.
125. Nicholls, L. and Y. Strengers, *Heatwaves, cooling and young children at home: Integrating energy and health objectives*. Energy Research & Social Science, 2018. **39**: p. 1-9.

CHAPTER 3: EXPERIMENTAL STUDY ONE

An assessment of skin temperature over the carotid artery as non-invasive core temperature monitoring site in premature infants under radiant warmers

Mohammad Fauzan Bin Maideen¹, James W Smallcombe¹ Kiran Kumar Balegar Virupakshappa²,
Erica Motyka², Ralph Nanan^{2, 3}, Ollie Jay^{1, 4}

¹ The University of Sydney, Thermal Ergonomics Laboratory, School of Health Sciences,
Faculty of Medicine and Health, Sydney, Australia

²Neonatal Intensive Care Unit, Nepean Hospital, Penrith
NSW, Australia

³Nepean Clinical School, Nepean Hospital, Sydney Medical School, University of Sydney
NSW, Australia

⁴The University of Sydney, Charles Perkins Centre, Sydney, NSW, Australia

Author contributions: MFBM, KKBV, EM, RN and OJ conceived and designed experiments; MFBM performed experiments; MFBM and JS analysed data; MFBM, JS and OJ interpreted data; MFBM and JS drafted manuscript; MFBM, JS and OJ edited/revised manuscript; MFBM, JS, KKBV, EM, RN and OJ approved final draft of manuscript (Appendix A).

Introduction

Owing to their immature thermoregulatory system and unique morphological features, neonates, especially if born prematurely, are susceptible to hypothermia [1]. An inability to maintain a stable normothermic core temperature over an extended time can lead to substantial health consequences that include a lower probability of survival [2]. Indeed, hypothermia, defined as core temperature of less than 36.5°C increases the risk of morbidity [3] and mortality [4, 5], and has been listed as the primary cause of infant death during the neonatal period by the World Health Organization [6]. External heat sources (e.g., radiant warmers) can be applied to prevent critical reductions in infant core temperature, but hyperthermia – a higher than optimal core temperature – can negatively affect an infant’s wellbeing and health [7, 8].

Adequately managing core temperature in newborn infants is therefore considered an essential component of neonatal intensive care. The most vulnerable neonates (i.e., pre-term, low birth-weight infants) are often nursed in a Neonatal Intensive Care Unit (NICU), with their body temperature managed with the use of an open-bed infant radiant warmers. Such devices are the preferred approach as they enable direct and easy access for nursing staff [9, 10]. The goal of these warmers is to compensate for any net heat loss between the infant and surrounding environment by delivering supplemental radiant heat and ensure that the infants remain in heat balance, and thus maintain a stable core temperature [11]. Typically, radiant heat output of these warmers is regulated by a servo-controlled feedback temperature measured by a single local skin temperature placed over the mid-axillary line (T_{feedback}). However, previous studies from our research team have shown that this method leads to cyclical bouts of heat debt and heat storage and large subsequent fluctuations in core temperature [12]. In some cases this simplistic method of regulating radiant warmer output can even lead to accidental bouts of potentially dangerous

overheating [13]. The underlying problem appears to be that, for both physiological and morphological reasons, the standard skin temperature measurement site often varies independently of true core temperature.

Core temperature can be monitored directly using invasive measures, such as with sensors placed in the rectum, nasopharynx, or oesophagus. However, rectal temperature probes can occasionally cause traumatic injury in neonates [14, 15], while nasopharyngeal probes can lead to mild-to-severe epistaxis [16, 17]. All invasive temperature measures therefore also carry some risk of their own and should be used as sparingly as possible if a safer, but similarly accurate, non-invasive measure is available. A study by our research group showed that a feasible non-invasive approach may be a temperature sensor placed on the skin of the neck (T_{neck}) over the carotid artery – a large blood vessel carrying warm freshly oxygenated blood to the head [18]. The study showed that T_{neck} served as a more accurate non-invasive estimate of core temperature than the traditional T_{feedback} measurement site in paediatric patients (aged 0 to 36 months) under general anaesthesia during elective surgery [18]. This T_{neck} measure could serve as a better feedback temperature for controlling radiant warmer output. However, blood flow is distributed in greater proportions to the periphery under general anaesthesia [19], which may make this method suitable in surgical settings but less so in non-anesthetised infants such as neonates nursed under radiant warmers.

Therefore, the aim of this study was to assess the suitability and level of agreement of T_{neck} as a surrogate measure of an invasive core temperature (rectal temperature, T_{rec}) in infants nursed under a radiant warmer. It was hypothesized that the level of agreement with T_{rec} would be superior with T_{neck} compared to T_{feedback} .

Methods

Participants

All experimental trials were conducted at the Nepean Hospital (Kingswood, NSW, Australia). Ethical approval was obtained from the Human Research Ethics Committee of the Nepean Blue Mountains Local Health District (HREC/17/NEPEAN/06). The authors declare that the study was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki. No adverse medical events occurred during, or following, the study.

41 infants (23 males, 18 females) between the postnatal age of 0 and 30 days undergoing standard Neonatal Intensive Care Unit (NICU) care at the Nepean Hospital were recruited upon entry into the NICU under the supervision of one of the researchers (KKBV) in our study, between August 2017 to May 2019 (see Table 1). Written and informed consent were obtained from the parents or guardians of these infants to participate in the study. Infants were included if their gestational ages were greater than 28 weeks irrespective of birth weight and were deemed stable to undergo continuous temperature monitoring under a standard infant radiant warmer (Giraffe Warmer, GE Healthcare, Australia). Infants were excluded if they had medical conditions that would have confounding thermoregulatory effects e.g. hypoxic-ischemic encephalopathy, neonatal sepsis; were immuno-compromised, were on breathing support or oxygen requirement via intubation and mechanical ventilation, considered critically ill by the medical team or had malformations that may preclude the placement of skin temperature sensors or the rectal temperature probe e.g. skin lesions, gastroschisis.

Table 1. Infant characteristics.

	Mean	SD
Postnatal age (days)	20	20
Gestational age (weeks + days)	33+3	3+1
Weight (g)	2120	646
Length (cm)	43.3	4.6
Body surface area (m²)*	0.16	0.03
Mean skinfold thickness (mm)	1.43	0.07

**Formula to calculate body surface area (m²): weight[kg]^{0.425} x height[cm]^{0.725} x 0.007184 (Du Bois & Du Bois, 1916)*

Instrumentation

The radiant warmer servo-control temperature was regulated by the infant's local skin temperature measured at a single point over the mid-axillary line (T_{feedback}) midway between the axilla and last rib, using the Giraffe warmer's skin thermistor (GE Healthcare, Australia) in line with the standard care procedures of the NICU and attached to the infant's skin by a qualified registered nurse. Skin temperature was measured using skin surface thermistors (YSI400 series thermistors) over the left side of the body at eight standardized anatomical sites: skin of the neck over the carotid artery (T_{neck}), forehead (T_{forehead}), abdomen (T_{abdomen}), chest (T_{chest}), back (T_{back}), thigh (T_{thigh}), foot (T_{foot}) and upper arm (T_{arm}). These thermistors were secured to the skin sites using hypoallergenic tape (Hypafix, Smith & Nephew, USA) and were insulated using gold reflective discs (Cardinal Health, USA) to avoid the thermistors from conducting any radiant heat from the radiant warmer (see Figure 1). A flexible rectal temperature sensor (TM400, Covidien, Mansfield, Massachusetts, USA) was inserted by the nursing staff to a depth of 3 cm past the anal sphincter and used to determine core body temperature (T_{rec}). Additionally, a pulse oximeter (Masimo Radical-7 series, Switzerland) was attached to the anterior surface of the right foot using

hypoallergenic tape (Hypafix, Smith &Nephew, USA) to continuously measure arterial oxygen saturation and heart rate.



Figure 1. Skin sensor placement sites on an infant participant.

Protocol

Before commencing data collection, anthropometric data (head circumference, length, age, gestational age and sex) were recorded by hand from the participant's chart to a standardized trial sheet. The radiant warmer (Giraffe Warmer, GE Healthcare, Australia) was used only for the participants in this study for data collection purposes and was not used for day-to-day nursing care. The radiant warmer was then switched on to the manual mode for approximately 15 minutes to warm up the device, as per usage guidelines. The infant was then transferred from his/her bassinet or humidity crib onto the radiant warmer mattress, which is made of medium density polyurethane foam secured by a waterproof, tear-resistant polyvinyl cover. The radiant warmer was then set to servo-control mode. Skinfold thickness at four sites (biceps, triceps, subscapular and suprailiac) was measured by a member of the NICU nursing staff using a standard skin caliper (Slim Guide, Michigan, USA). The infant was then weighed, using the Giraffe warmer's in-built weighing function. Apart from wearing diapers, the infant did not wear any clothing throughout the data collection session. The infant was placed in the centre of the radiant warmer bed to ensure that the positioning of the infant was within the radiant field throughout the data collection session (see Figure 2). Data collection began with thermometric values sampled at 10-s intervals via a data acquisition box (NI cDAQ-91722 module, National Instruments, Austin, TX, USA) and displayed in real-time via a laptop using LabView software (version 7.0). For safety purposes, heart rate and oxygen saturation were monitored continuously, and blood pressure (Welch-Allyn, USA) was assessed before and after the observation period.



Figure 2. Positioning of an infant participant under the radiant warmer.

All regular nursing interventions by the NICU staff (i.e., adjusting of pulse oximeter, diaper changes) were allowed during the data collection process and were noted down by a study researcher (MFBM) who was present with the infant throughout the data collection session. The infant was otherwise left undisturbed. Unless nursing care instructions required the infant to remain in the supine position throughout, the infant was initially placed in the supine position and turned over to prone positioning midway through the data collection period. Upon completion of data collection, the nursing staff removed all instrumentation and the infant was reweighed. The infant was then transferred back to their bassinet or crib and regular NICU nursing care resumed. Measurements were taken for one session only, with a mean duration of $204(\pm 30.4)$ min, up to a maximum duration of 240 min. Environmental parameters within the NICU were measured using a Kestrel 5400 series (Nielsen-Kellerman, Pennsylvania, USA) portable unit secured onto a drip stand next to the radiant warmer away from its radiant field; ambient temperature was recorded as $23.5 \pm 1.0^\circ\text{C}$ and ambient humidity as $45 \pm 8\%$.

Statistical Analysis

Bland-Altman plots were used to assess the agreement between the T_{neck} and T_{rec} by calculating the mean bias and limits of agreement (LoA) with our reference measure (T_{rec}) on the x-axis. The data was collected every ten seconds, and data artefacts were removed as part of the data cleaning process prior to analysis. The remaining 10-second interval data points were then averaged into 1-minute, 5-minute and 30-minute intervals. The 30-minute averaged measurements were then used as data points for the Bland-Altman analysis. As an example, an uninterrupted 240-minute observation without data artefacts will yield eight 30-minute-average data points for analysis.

The difference between T_{rec} and T_{neck} , with 95% probability, lies within the respective limits of agreement which was calculated for each participant every 30 min by multiplying the standard deviation of the mean difference between T_{neck} and T_{rec} by 1.96. The acceptable limits of agreement were determined a priori as $\pm 0.5^{\circ}\text{C}$ [20]. Statistical analyses were performed using GraphPad Prism Version 7.02 for Windows (GraphPad Software, La Jolla, CA, USA).

Results

Due to technical issues with equipment, 6 data sets were not suitable for analysis. In total, data from 35 infants (18 males, 17 females) were included in the analysis, yielding 223 observations (196 in supine position, 27 in prone position) in total with data collected with the infants in both positions combined for analysis.

The mean bias, when comparing T_{neck} and T_{feedback} values against T_{rec} values were $-0.16 \pm 0.38^{\circ}\text{C}$ (95% LoA= -0.84 to $+0.53^{\circ}\text{C}$) for T_{neck} and $-0.46 \pm 0.38^{\circ}\text{C}$ (95% LoA= -1.21 to $+0.29^{\circ}\text{C}$) for T_{feedback} . Based on the acceptable limits of agreement determined *a priori*, 82.1% of T_{neck} and 54.7% of T_{feedback} values were within $\pm 0.5^{\circ}\text{C}$ of T_{re} (see Figure 3). Above a true core temperature (measured rectally) of $\sim 37.0^{\circ}\text{C}$, T_{feedback} systematically underestimated T_{rec} by $>0.5^{\circ}\text{C}$, with this error growing as infants approached hyperthermic levels of core temperature to the extent that at a T_{rec} of 38.0°C , the error between T_{feedback} and T_{rec} was $\sim 1.5^{\circ}\text{C}$, i.e., the infant was hyperthermic, but according to T_{feedback} value the infant would have been incorrectly assessed as being normothermic.

The inter-individual variability in the difference between T_{neck} and T_{rec} was not significantly associated ($P > 0.15$) with body mass, body surface area, body mass to surface area ratio or the mean skinfold thickness. In contrast, the inter-individual variability in the difference

between T_{feedback} and T_{rec} associated significantly ($P < 0.01$) with body surface area and mean skinfold thickness, but together these variables described only 14% of the total variance observed.

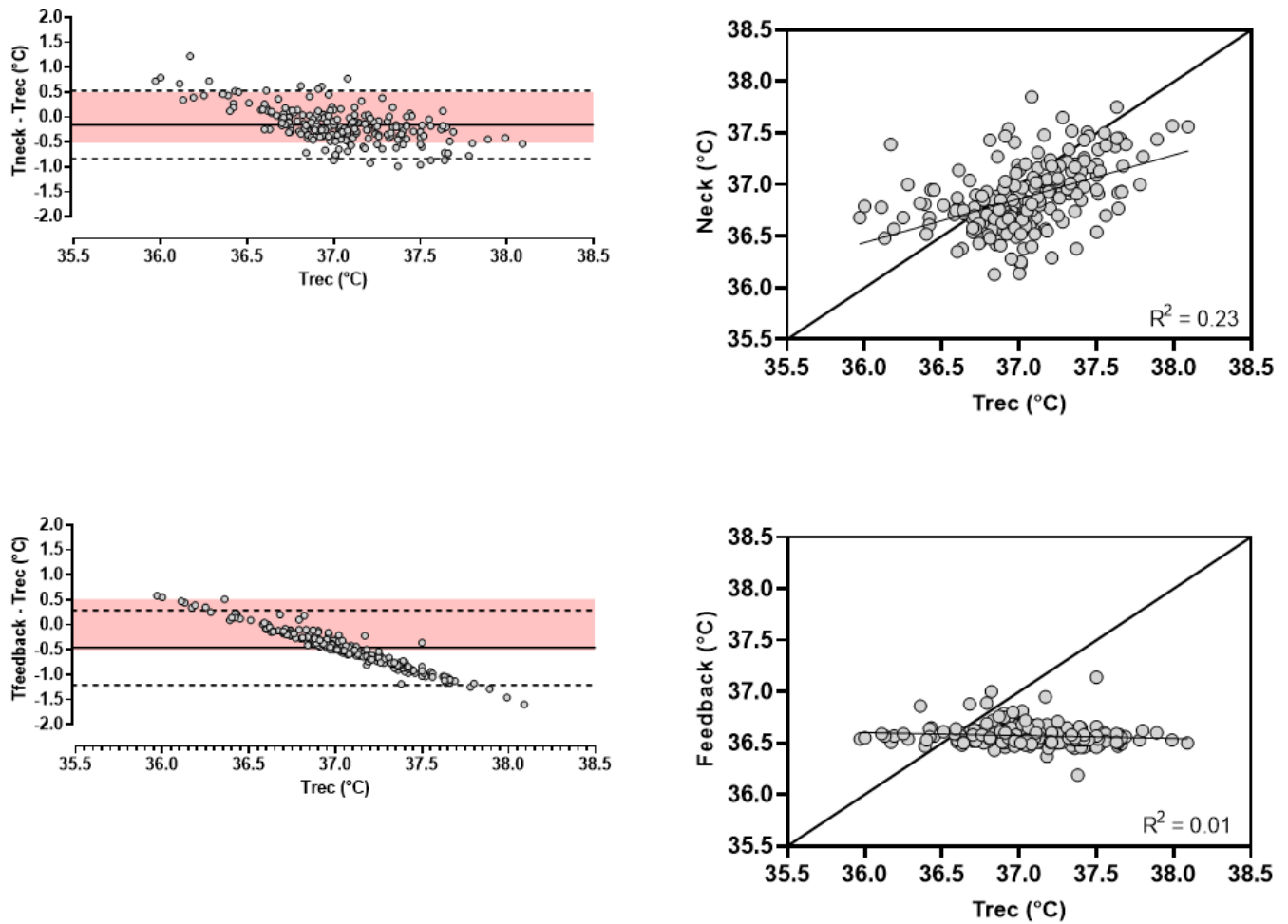


Figure 3. Left: Bland-Altman plots illustrating the mean bias (solid line) and 95% confidence intervals (± 1.96 s.d.: dotted lines) for measured rectal temperature (T_{rec}) vs the difference between rectal temperature and skin temperature measured on the neck (T_{neck}) and the servo-feedback temperature sensor of the radiant warmer positioned at the mid-axillary line (T_{feedback}). The red band indicates the *a priori* acceptable limits of agreement (± 0.5 $^{\circ}\text{C}$) for estimating core temperature. **Right:** Simple regression analysis of the relationship between absolute T_{neck} , T_{feedback} with absolute T_{rec} .

Discussion

This study examined the levels of agreement of skin temperature measured over the carotid artery (T_{neck}) as a surrogate measure of core body temperature when compared to the conventional mid-axillary skin sensor placement (T_{feedback}) on infants nursed under a radiant warmer. The main finding demonstrated that T_{neck} exhibited a superior level of agreement compared to T_{feedback} regardless of infant position, however, there was a tendency for both skin temperature sites to underestimate core temperature when compared with T_{rec} . In the relatively rare instances in which T_{rec} exceeded 37.5°C (i.e. mild hyperthermia), the temperature measurements obtained from T_{neck} more often remained within the acceptable limit of $\pm 0.5^{\circ}\text{C}$ of T_{rec} , whereas much larger underestimations of T_{rec} were derived from T_{feedback} which could in turn increase the risk of undetected infant hyperthermia in ICU settings.

When the conventionally used T_{feedback} was compared to T_{rec} only 54.7% of measurements fell within the acceptable limits of $\pm 0.5^{\circ}\text{C}$, as determined *a priori*, with a mean bias of -0.46°C ($R^2 = 0.01$). Although substantial variability between measurement methods remained ($R^2 = 0.23$), the mean bias was substantially reduced when T_{neck} was measured with 82.1% measurements falling within $\pm 0.5^{\circ}\text{C}$ of T_{rec} with a mean bias of -0.16°C . This mean bias for T_{neck} is slightly smaller than the mean bias (-0.52°C) observed between skin temperature measured over the carotid artery and nasopharyngeal temperature in infants under general anaesthesia – before a correction factor was applied [18]. The authors of this previous study attributed the good agreement of these two temperatures measurement sites to the close proximity of the T_{neck} measurement to a major artery which runs close to the skin's surface [18]. Whilst skin temperature measured near the axilla can in theory represent the temperature of the axillary artery, it can be influenced by a several factors

including skin blood flow alterations [21] and ipsilateral intravenous infusion [22] and more likely provides an indication of peripheral temperature [23]. It is possible that the smaller mean bias between T_{neck} and T_{rec} observed in the current study was attributable to the high radiant heat flux from radiant warmer which is positioned near the head and neck. This source of radiant heat likely increased local skin temperatures in these regions [13], reducing the temperature gradient between the skin and the core and, therefore, the measurement differences observed.

Clinical Practice Considerations

Previous studies [12, 18] have explored using the neck site as an alternative non-invasive method to measure skin temperature in infants and children who were sedated, either in the operating theatre or in the NICU. However, in the current study, the increased motor activity of the conscious infants did not adversely affect the temperature measurements obtained from the T_{neck} sensor, which was adhered securely in-line with standard nursing practices using hypoallergenic tape. This study clearly demonstrates that the neck site is a clinically preferable alternative to the commonly used feedback sensor placement when infants are nursed under a radiant warmer. Additionally, due to the presence of the neck skin folds, the researchers also observed that there may be an additional insulative component to the site as fold of skin often at least partially cover the temperature sensors attached to the neck. In addition to the superior agreement with T_{rec} , the neck site is also a practical alternative to T_{feedback} as it is easily accessed when nursing an infant, especially when in the supine position. The T_{neck} temperature sensor is also less likely to be dislodged due to arm movements when the infant is awake. The T_{neck} measurement site may also be used on infants who are non-sedated but critically ill as it may help minimise

disturbance to the infant, especially those who are irritable, very ill and do not cope well physiologically with interruptions as part of their routine clinical care.

Limitations

Limitations of the study include the fact that the infants were of a relatively narrow postnatal age range (4 to 97 days), and therefore access to the skin area over the carotid artery site may appear to be challenging due to presence of skin folds adjacent to the neck area, relative to the infant's size [24]. However, during the process of data collection, the nursing staff anecdotally did not express concerns nor difficulties in locating and adhering the skin sensor thermistors, and it was observed that the hypoallergenic tape used sufficed to ensure that neck sensor stayed in its place throughout the data collection. Furthermore, in instances when there was a need to change the tape (e.g., cleaning of milk accumulation within the neck folds post bottle feeding), the process did not disturb the infant's resting state due to the accessibility of the site. Access to the neck region may have its limitations with infants born with web neck anomalies or excessive neck skin folds [25, 26], however this will need further investigation to determine the efficacy of the T_{neck} measurement technique in this unique population. Lastly, the authors acknowledge that the acceptable limit of agreement (LoA) predetermined at $\pm 0.5^{\circ}\text{C}$ will have different physiological consequences depending on the absolute core temperature, especially in the hyperthermic range, from a heat-illness perspective. The data, however, indicated that the hyperthermic range was not a reason for concern in our analysis, as nearly 99% of all observed data points of absolute core temperature (Figure 3) were less than 38°C . As a result, the risk of hyperthermia is negligible to zero.

Conclusion

Our findings have clearly demonstrated that in infants nursed under a radiant warmer, the placement of the skin sensor over the carotid artery yielded a higher level of agreement to rectal temperature compared with the traditional placement of the feedback sensor along the mid-axillary line, regardless of infant position. Therefore, this study challenges the commonly used method of skin sensor feedback placement in clinical practice. However, despite the improved level agreement exhibited by T_{neck} , a systematic underestimation of T_{rec} was still observed which could lead the inaccurate assessment of an infant's thermal state. Future research is therefore required to further optimise the estimation of core temperature via more accurate non-invasive measurements.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

The authors would like to acknowledge Chris Hargans, Senior Technical Officer (NICU, Nepean Hospital) for technical support rendered during the data collection period.

Experimental Study One References

1. Vohra, S., et al., *Heat Loss Prevention (HeLP) in the delivery room: A randomized controlled trial of polyethylene occlusive skin wrapping in very preterm infants*. The Journal of Pediatrics, 2004. **145**(6): p. 750-753.
2. World Health Organisation, *WHO recommendations on interventions to improve preterm birth outcomes*, W.L.C.-i.-P. Data, Editor. 2015. p. 108.
3. Hannenberg, A.A. and D.I. Sessler, *Improving perioperative temperature management*. Anesthesia and Analgesia, 2008. **107**(5): p. 1454-1457.
4. Laptook, A.R. and M. Watkinson, *Temperature management in the delivery room*. Seminars in Fetal and Neonatal Medicine, 2008. **13**(6): p. 383-391.
5. Narendran, V. and S.B. Hoath, *Thermal management of the low birth weight infant: A cornerstone of neonatology*. The Journal of Pediatrics, 1999. **134**(5): p. 529-531.
6. WHO, *Thermal Protection of the Newborn: a practical guide*. 1997, World Health Organisation: Geneva.
7. Baumgart, S., *Iatrogenic hyperthermia and hypothermia in the neonate*. Clinics in Perinatology, 2008. **35**(1): p. 183-97, ix-x.
8. Laptook, A.R., et al., *Admission Temperature of Low Birth Weight Infants: Predictors and Associated Morbidities*. Pediatrics, 2007. **119**(3): p. e643.
9. Flenady, V. and P.G. Woodgate, *Radiant warmers versus incubators for regulating body temperature in newborn infants (review)*. Cochrane Database of Systematic Reviews, 2009(2): p. 1-41.
10. Fic, A.M., et al., *Heat and mass transfer under an infant radiant warmer--development of a numerical model*. Medical Engineering and Physics, 2010. **32**(5): p. 497-504.
11. Bell, E.F., *Infant incubators and radiant warmers*. Early Human Development, 1983. **8**(3): p. 351-375.

12. Molgat-Seon, Y., et al., *Assessing neonatal heat balance and physiological strain in newborn infants nursed under radiant warmers in intensive care with fentanyl sedation.* European Journal of Applied Physiology, 2014. **114**(12): p. 2539-49.
13. Molgat-Seon, Y., et al., *Accidental overheating of a newborn under an infant radiant warmer: a lesson for future use.* Journal of Perinatology, 2013. **33**(9): p. 738-9.
14. Christensen, R.D., T.J. Pysher, and S.S. Christensen, *Case report: perianal necrotizing fasciitis in a near-term neonate.* Journal of Perinatology, 2007. **27**(6): p. 390-391.
15. Frank, J.D. and S. Brown, *Thermometers and rectal perforations in the neonate.* Archives of Disease in Childhood, 1978. **53**(10): p. 824-5.
16. Kumar, P.A. and H. Arora, *Potential aspiration hazard when using a nasopharyngeal temperature probe with disposable cover.* Journal of Clinical Anesthesia, 2006. **18**(7): p. 556-557.
17. Sinha, P.K., S. Kaushik, and P.K. Neema, *Massive epistaxis after nasopharyngeal temperature probe insertion after cardiac surgery.* Journal of Cardiothoracic and Vascular Anesthesia, 2004. **18**(1): p. 123-4.
18. Jay, O., et al., *Skin temperature over the carotid artery provides an accurate noninvasive estimation of core temperature in infants and young children during general anesthesia.* Paediatric Anaesthesia, 2013. **23**(12): p. 1109-16.
19. Matsukawa, T., et al., *Heat Flow and Distribution during Induction of General Anesthesia* Anesthesiology, 1995. **82**(3): p. 662-673.
20. Kimberger, O., et al., *Accuracy and precision of a novel non-invasive core thermometer.* British Journal of Anaesthesia, 2009. **103**(2): p. 226-31.
21. Holtzclaw, B.J., *Monitoring body temperature.* . AACN Clinical Issues in Critical Care Nursing, 1993. **4**: p. 44-55.

22. Bissonnette, B., *Pediatric Anesthesia: Basic Principles*, in *Temperature Regulation: physiology and pharmacology*, B. Bissonnette, Editor. 2011, People's Medical Publishing House-USA: Shelton, CT. p. 221-258.
23. Gunga, H.-C., *Desert and tropical environments*, in *Human physiology in extreme environments*, H.-C. Gunga, Editor. 2021, Academic Press: London, England. p. 169-221.
24. Olsen, I.E., et al., *Use of a Body Proportionality Index for Growth Assessment of Preterm Infants*. The Journal of Pediatrics, 2009. **154**(4): p. 486-491.
25. Roberts, A.E., et al., *Noonan syndrome*. The Lancet, 2013. **381**(9863): p. 333-342.
26. Sybert, V.P. and E. McCauley, *Turner's Syndrome*. The New England Journal of Medicine, 2004. **351**(12): p. 1227-1238.

CHAPTER 4: BRIDGING STATEMENT

The first experimental study demonstrated that the placement of the skin temperature sensor over the carotid artery yielded a higher level of agreement to rectal temperature, compared with the traditional placement of the feedback sensor along the mid-axillary line, regardless of infant position, in infants nursed under a radiant warmer. However, there was still an observed systematic underestimation of core temperature measured in the rectum (T_{rec}). Thus, the objective of the next chapter of this thesis was to investigate a different non-invasive measurement technique that might be able to further reduce this underestimation: zero heat flux thermometry. This method of estimating deep core temperature is based on the theory that if the skin surface is highly insulated, heat loss from the body's skin surface will be reduced to zero, and therefore the gradient between deeper tissue temperatures and the skin surface temperature will be diminished, resulting in a skin surface temperature that resembles core body temperature better than the methods reported in the previous chapter [1-3]. While the zero heat flux method has been shown to be of limited utility for use with adults [4-5], because infants exhibit lower levels of subcutaneous fat and their body tissues reside at a shallower depth, it can be assumed that the thermal gradient between a newborn's skin and body core is lower than that of an adult [6]. For this reason, the zero-heat flux approach is a potentially feasible concept in the infant population in the NICU setting.

The experimental study that will be discussed in the following chapter of this thesis will assess the suitability and level of agreement of potential skin contact temperature sites, using the zero-heat flux approach, as optimal surrogate measures of (T_{rec}), when these infants are nursed either in supine or prone, under a radiant warmer.

Bridging Statement References

1. Fox, R.H., et al., *A New Method for Monitoring Deep Body Temperature from the Skin Surface*. Clinical Science and Molecular Medicine, 1973. **44**(1): p. 81-86.
2. Togwa, T., et al., *A modified internal temperature measurement device*. Medical & Biological Engineering, 1976. **14**(3): p. 361-364.
3. Yamakage, M. and A. Namiki, *Deep temperature monitoring using a zero-heat-flow method*. Journal of Anesthesia, 2003. **17**: p. 108-115.
4. Eshraghi, Y., et al., *An Evaluation of a Zero-Heat-Flux Cutaneous Thermometer in Cardiac Surgical Patients*. Anesthesia and Analgesia, 2014. **119**: p. 543-9.
5. Teunissen, L.P.J., et al., *Non-invasive continuous core temperature measurement by zero heat flux*. Physiological Measurement, 2011. **32**: p. 559-570.
6. Hey, E.N. and G. Katz, *The Range of Thermal Insulation in the Tissues of the New Born Baby*. Journal of Physiology, 1970. **207**: p. 667-681.

CHAPTER 5: EXPERIMENTAL STUDY TWO

**An evaluation of skin contact temperature as a non-invasive method for monitoring
core temperature in premature infants under radiant warmers**

Mohammad Fauzan Bin Maideen^{1,2}, James W Smallcombe^{1,2}, Kiran K Balegar
Virupakshappa³, Erica Motyka³, Ralph Nanan^{3, 4}, Ollie Jay^{1, 2}

¹ The University of Sydney, Thermal Ergonomics Laboratory, School of Health Sciences,
Faculty of Medicine and Health, Sydney, Australia

² Heat and Health Research Incubator, The University of Sydney, Sydney, NSW, Australia

³ Neonatal Intensive Care Unit, Nepean Hospital, Penrith
NSW, Australia

⁴ Nepean Clinical School, Nepean Hospital, Sydney Medical School, University of Sydney
NSW, Australia

Author contributions: MFBM, KKBV, EM, RN and OJ conceived and designed experiments; MFBM performed experiments; MFBM and JS analysed data; MFBM, JS and OJ interpreted data; MFBM and JS drafted manuscript; MFBM, JS and OJ edited/revised manuscript; MFBM, JS, KKBV, EM, RN and OJ approved final draft of manuscript (Appendix B).

Introduction

In humans, body temperature is physiologically regulated within a narrow range around $\sim 37^{\circ}\text{C}$ by balancing the rate of metabolic heat production with the rate of net heat transfer to the external environment. Neonates find it particularly difficult to maintain normothermia [1] especially infants who were born preterm (births occurring between the 22nd and the 37th week of gestation) and infants with low birthweight (LBW) (newborns with a birth weight of less than 2500g) as they do not have sufficiently mature thermoregulatory systems to allow them to cope with changes in their thermal environment [2]. Despite neonates having a relative abundance of brown adipose tissue, they have a low capacity to produce metabolic heat via shivering [3]. In addition, they possess limited vasomotor activity, a surface area-to-mass ratio four times greater than a typical adult, experience evaporative heat loss through the skin via transdermal water loss and that behavioural thermoregulatory responses are also non-existent [3], making them susceptible to hypothermia.

A prolonged failure to maintain thermal homeostasis has profound health consequences and as such, following delivery, the nursing of newborn babies in warmer environments has been demonstrated to promote better survival [4], including recommendations made to address thermal care in improving preterm birth outcomes [5]. Hypothermia, defined as core body temperature lower than 36.5°C [6], results in greater infant morbidity [7] and mortality [8, 9], and has been listed as the primary cause of infant death during the neonatal period by the World Health Organization [6]. Furthermore, prolonged hypothermia has been linked to hypoglycaemia, respiratory distress, hypoxia, metabolic acidosis [10-12] and overall negative clinical outcomes in neonates [13]. Hyperthermia, on the other hand, can also be harmful to a newborn's health as febrile neonates have higher rates of morbidity and mortality [14, 15].

As such, body temperature management is regarded as an essential component of neonatal intensive care. The most vulnerable neonates (i.e., pre-term, low birth-weight infants)

are often nursed in a Neonatal Intensive Care Unit (NICU) under open-bed infant radiant warmers to simultaneously maintain their thermal status and provide direct and easy access for nursing staff [16, 17]. These warmers seek to deliver residual radiant heat such that the rate of net heat transfer from the neonate to the surrounding environment via convection, conduction, evaporation, and radiation balances the rate of metabolic heat production, resulting in a stable internal body temperature [18]. The system employed to regulate the intensity of radiant heat output from these warmers is therefore critical since too much or too little heat delivery can rapidly evolve into neonatal hyperthermia and hypothermia, respectively [18]. Presently, radiant heat output on most radiant warmer devices is regulated according to a servo-controlled feedback signal from a single local skin temperature measured over the mid-axillary line (T_{feedback}). However, studies have demonstrated that the present system results in transient, cyclical bouts of heat debt and heat storage and consequent fluctuations in deep core temperature, resulting in the neonates exhibiting physiological strain and has the potential to lead to an accidental bout of overheating [19]. Moreover, large variations in local skin temperatures (e.g., chest, feet) have been observed despite the tight regulation of T_{feedback} , and a poor agreement between T_{feedback} and deep core temperature measured in the rectum (T_{rec}) [20]. An earlier study by our group showed that a temperature sensor placed on the neck (T_{neck}) in paediatric patients under general anaesthesia during elective surgery potentially serves as a more accurate non-invasive estimate of core temperature in infants compared to the current T_{feedback} method [21], however the level of accuracy remains insufficient to safely regulate radiant warmer output. An alternate approach is therefore still required.

Zero heat flux is a method to estimate deep core temperature by creating an almost perfectly insulated area near the skin, with the assumption that if heat loss from the skin surface of the body is reduced to zero, the gradient between deep core temperature and skin surface temperature will tend toward zero [22, 23]. The surface temperature of this area of skin will equilibrate with the deep core temperature [22, 23]. Studies have investigated using zero heat

flux method in clinical scenarios such as with infants, and in surgical and intensive care settings [24-26], however none to date has examined this method when monitoring an infant under a radiant warmer for continuous long-term monitoring. A potential solution under this scenario may be the utilisation of the skin sites that commonly serve as contact temperature points with a mattress, which acts as an effective insulator. This approach may constitute a temperature sensor placed on the back (T_{back}) for when an infant is supine, and a separate sensor placed on the chest (T_{chest}) for when the infant is prone.

Therefore, the aim of this study was to assess the suitability and level of agreement of potential skin contact temperature sites i.e., T_{back} (when an infant is supine) or T_{chest} (when an infant is prone) as a surrogate measure of core temperature measured in the rectum (T_{rec}) in infants nursed under a radiant warmer. It was hypothesized that the level of agreement with T_{rec} would be superior with T_{back} (when supine) and T_{chest} (when prone) compared to T_{feedback} .

Methods

Participants

All experimental trials were conducted at the Nepean Hospital (Kingswood, NSW, Australia). Ethical approval was obtained from the Human Research Ethics Committee of the Nepean Blue Mountains Local Health District (HREC/17/NEPEAN/06). The authors declare that the study was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki. No adverse medical events occurred during, or following, the study.

In total, 41 infants (23 males, 18 females) between the postnatal age of 0- and 30-days undergoing standard Neonatal Intensive Care Unit (NICU) care at the Nepean Hospital were recruited upon entry into the NICU under the supervision of one of the researchers (KKBV) in our study (see Table 1). Written and informed consent was obtained from the parents or guardians of these infants to participate in the study. Infants were included if their gestational ages were greater than 28 weeks irrespective of birth weight and were deemed stable to undergo continuous temperature monitoring under a standard infant radiant warmer (Giraffe Warmer, GE Healthcare, Australia). Infants were excluded if they had medical conditions that would have confounding thermoregulatory effects e.g., hypoxic-ischemic encephalopathy, neonatal sepsis; were immuno-compromised, were on breathing support or oxygen requirement via intubation and mechanical ventilation, considered critically ill by the medical team or had malformations that may preclude the placement of skin temperature sensors or the rectal temperature probe e.g., skin lesions, gastroschisis.

Table 1. Infant characteristics.

	Mean	SD
Postnatal age (days)	20	20
Gestational age (weeks + days)	33+3	3+1
Weight (g)	2120	646
Length (cm)	43.3	4.6
Body surface area (m²)	0.16	0.03
Mean skinfold thickness (mm)	1.43	0.07

**Formula to calculate body surface area (m²): weight[kg]^{0.425} × height[cm]^{0.725} × 0.007184 (Du Bois & Du Bois, 1916)*

Instrumentation

The radiant warmer servo-control temperature was regulated by the infant's local skin temperature measured at a single point over the mid-axillary line (T_{feedback}) midway between the axilla and last rib, in line with the standard care procedures of the NICU and attached by a qualified registered nurse. Skin temperature was measured using skin surface thermistors (YSI400 series thermistors) over the left side of the body at eight standardized anatomical sites (Figure 1): forehead (T_{forehead}), abdomen (T_{abdomen}), chest (T_{chest}), back (T_{back}), thigh (T_{thigh}), foot (T_{foot}) and upper arm (T_{arm}) (see Figure 1). These thermistors were secured to the skin sites using hypoallergenic tape (Hypafix, Smith & Nephew, USA) and were insulated using gold reflective discs (Cardinal Health, USA) to avoid the thermistors from conducting any radiant heat from the radiant warmer. Mean skin temperature (T_{sk}) was expressed as a weighted average in accordance with Klein and Scammon [27]. A flexible rectal temperature sensor (TM400, Covidien, Mansfield, Massachusetts, USA) was inserted by the nursing staff to a depth of 3 cm past the anal sphincter and used to determine core body temperature (T_{rec}). Additionally, a pulse oximeter (Masimo Radical-7 series, Switzerland) was attached to the anterior surface of the right foot using hypoallergenic tape (Hypafix, Smith & Nephew, USA) to continuously measure arterial oxygen saturation and heart rate.

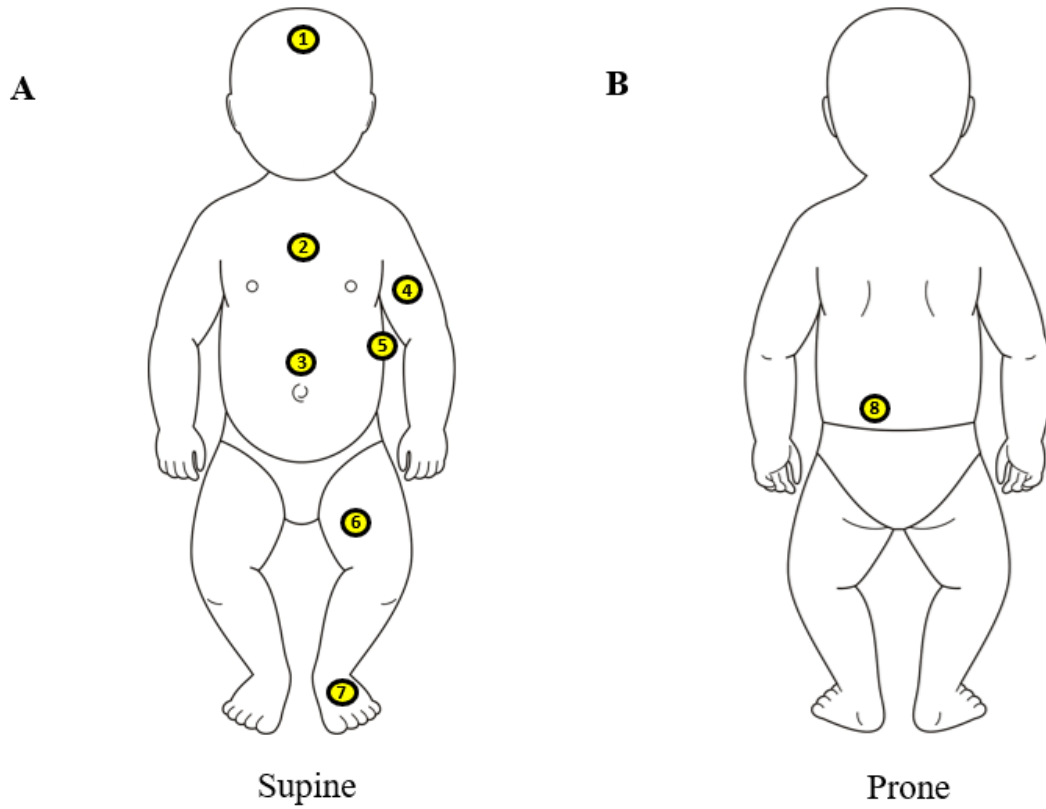


Figure 1. Schematic diagram illustrating the skin sensor placements on the infant. **A.** Supine: 1 – T_{forehead} (centre of forehead); 2 - T_{chest} (centre of sternum); 3 – T_{abdomen} (upper abdomen); 4 - T_{arm} – (upper anterior arm); 5 – T_{feedback} (mid-axillary line at the lateral aspect of trunk); 6 – T_{thigh} (anterior thigh); 7. T_{foot} - (dorsum of foot). **B.** Prone: 8 – T_{back} (L4-L5 region at the paraspinal aspect).

Protocol

Before commencing data collection, anthropometric data (head circumference, length, age, gestational age and sex) were recorded by hand from the participant's chart to a standardized trial sheet. The radiant warmer (Giraffe Warmer, GE Healthcare, Australia) was used only for the participants in this study for data collection purposes and was not used for day-to-day nursing care. The radiant warmer was then switched on to the manual mode for approximately 15 minutes to warm up the device, as per usage instructions. The infant was then transferred from his/her bassinet or humidity crib onto the radiant warmer mattress, which is made of medium density polyurethane foam secured by a waterproof, tear-resistant polyvinyl cover. The radiant warmer was then set to servo-control mode. Skinfold thickness at four sites (biceps, triceps, subscapular and supriliac) was measured by a member of the NICU nursing staff using a standard skin caliper (Slim Guide, Michigan, USA). The infant was then weighed, using the Giraffe warmer's in-built weighing function. Apart from diapers, the infant did not wear any clothing throughout the data collection session. The infant was placed in the centre of the radiant warmer bed to ensure that the positioning of the infant was within the radiant field throughout the data collection session. Data collection began with thermometric values sampled at 10-s intervals via a data acquisition box (NI cDAQ-91722 module, National Instruments, Austin, TX, USA) and displayed in real-time via a laptop using LabView software (v7.0). For safety purposes, heart rate and oxygen saturation were monitored continuously, and blood pressure (Welch-Allyn, USA) was assessed before and after the observation period.

All regular nursing interventions by the NICU staff (i.e., adjusting of pulse oximeter, diaper changes) were allowed during the data collection process and were recorded by a study researcher (MFBM) who was present with the infant throughout the data collection session. The infant was otherwise left undisturbed. Unless nursing care instructions required the infant to remain in the supine position throughout, the infant was initially placed in the supine position and turned over to prone positioning midway through the observation period. Upon completion

of data collection, the nursing staff removed all instrumentation, and the infant was reweighed. The infant was then transferred back to their bassinet or crib and regular NICU nursing care resumed. Measurements were taken for one session only, with a mean duration of $204(\pm 30.4)$ min, up to a maximum of 240 min. Environmental parameters within the NICU were measured using a Kestrel 5400 series (Nielsen-Kellerman, Pennsylvania, USA) portable unit secured onto a drip stand next to the radiant warmer away from its radiant field; ambient temperature was recorded as $23.5\pm 1.0^{\circ}\text{C}$ and ambient humidity as $45\pm 8\%$.

Statistical Analysis

Bland-Altman plots were used to assess the agreement between the skin contact sites and T_{rec} by calculating the mean bias and limits of agreement (LoA) with our reference measure (T_{rec}) on the x-axis. The data was collected every ten seconds, and data artefacts were removed as part of the data cleaning process prior to analysis. The remaining 10-second interval data points were then averaged into 1-minute, 5-minute and 30-minute intervals. The 30-minute averaged measurements were then used as data points for the Bland-Altman analysis. As an example, an uninterrupted 240-minute observation without data artefacts will yield eight 30-minute-average data points for analysis.

The difference between T_{rec} vs. T_{back} ; T_{rec} vs. T_{chest} ; and T_{rec} vs. T_{feedback} with 95% probability, lies within the respective limits of agreement which was calculated for each participant every 30 min by multiplying the standard deviation of the mean difference between skin contact temperatures and T_{rec} by 1.96. The acceptable limits of agreement were determined a priori as $\pm 0.5^{\circ}\text{C}$ [28]. Statistical analyses were performed using GraphPad Prism Version 7.02 for Windows (GraphPad Software, La Jolla, CA, USA).

Results

Due to technical issues with equipment, 6 data sets were not suitable for analysis. In total, data from 35 infants (18 males, 17 females) were included in the analysis, yielding 196 and 27 observations in the supine and prone positions, respectively.

Supine position

The mean bias, when comparing $T_{\text{back}(\text{contact})}$ and T_{feedback} values against T_{rec} values were $-0.01 \pm 0.24^\circ\text{C}$ (95% LoA= -0.48°C to $+0.46^\circ\text{C}$) and $-0.45 \pm 0.39^\circ\text{C}$ (95% LoA= -1.20°C to $+0.31^\circ\text{C}$), respectively. Based on the acceptable limits of agreement determined *a priori*, 94.9% and 56.6% of $T_{\text{back}(\text{contact})}$ and T_{feedback} values within $\pm 0.5^\circ\text{C}$ of T_{rec} , respectively. Data pertaining to all other skin temperature sites are presented in Table 2. Figure 2 illustrates the Bland-Altman and correlation plots for $T_{\text{back}(\text{contact})}$ and T_{feedback} relative to T_{rec} in the supine position.

Table 2. Mean bias and 95% limits of agreement (LOA) for estimates of core body temperature (compared with rectal temperature) derived from different skin temperature sites in the supine and prone positions.

Temperature site	Mean bias ($^\circ\text{C} \pm \text{s.d}$)	95% LOA ($^\circ\text{C}$)	Points within $\pm 0.5^\circ\text{C}$
SUPINE (n=196)			
Back (contact)*	-0.01 ± 0.24	-0.48 to $+0.46$	94.9%
Chest	-0.41 ± 0.51	-1.42 to $+0.58$	58.2%
Mid-axillary (feedback)	-0.45 ± 0.39	-1.20 to $+0.31$	56.6%
Abdomen	-0.47 ± 0.65	-1.74 to $+0.80$	51.0%
Forehead	-0.82 ± 0.56	-1.92 to $+0.29$	27.0%
Mean Tsk	-0.84 ± 0.42	-1.67 to $+0.01$	21.4%
Upper Arm	-1.19 ± 0.65	-2.46 to $+0.08$	11.7%
Thigh	-1.30 ± 0.80	-2.87 to $+0.27$	11.2%
Foot	-2.53 ± 1.84	-6.13 to $+1.07$	2.0%
PRONE (n=27)			
Chest (contact)*	$+0.02 \pm 0.19$	-0.35 to $+0.39$	96.3%
Abdomen (contact)*	$+0.11 \pm 0.23$	-0.35 to $+0.56$	96.3%
Back	-0.29 ± 0.44	-1.16 to $+0.58$	63.0%
Mid-axillary (feedback)	-0.57 ± 0.35	-1.25 to $+0.11$	40.7%
Mean Tsk	-0.65 ± 0.28	-1.20 to $+0.10$	33.3%
Forehead	-0.87 ± 0.41	-1.67 to $+0.07$	22.2%
Upper Arm	-0.90 ± 0.50	-1.89 to $+0.09$	18.5%
Thigh	-1.16 ± 0.77	-2.67 to $+0.36$	14.8%
Foot	-1.96 ± 1.23	-4.38 to $+0.46$	3.7%

* Skin site in continuous contact with the radiant warmer mattress

Body mass, body surface area-to-mass ratio, mean skinfold thickness and the absolute back skin temperature did not significantly ($P > 0.05$) associate with the inter-individual variability in the difference between $T_{\text{back}(\text{contact})}$ and T_{rec} .

In contrast, the inter-individual variability in the difference between T_{feedback} and T_{rec} associated significantly ($P < 0.05$) with body mass, mean skin fold thickness and absolute T_{feedback} , together explaining 22.6% of the total variance observed.

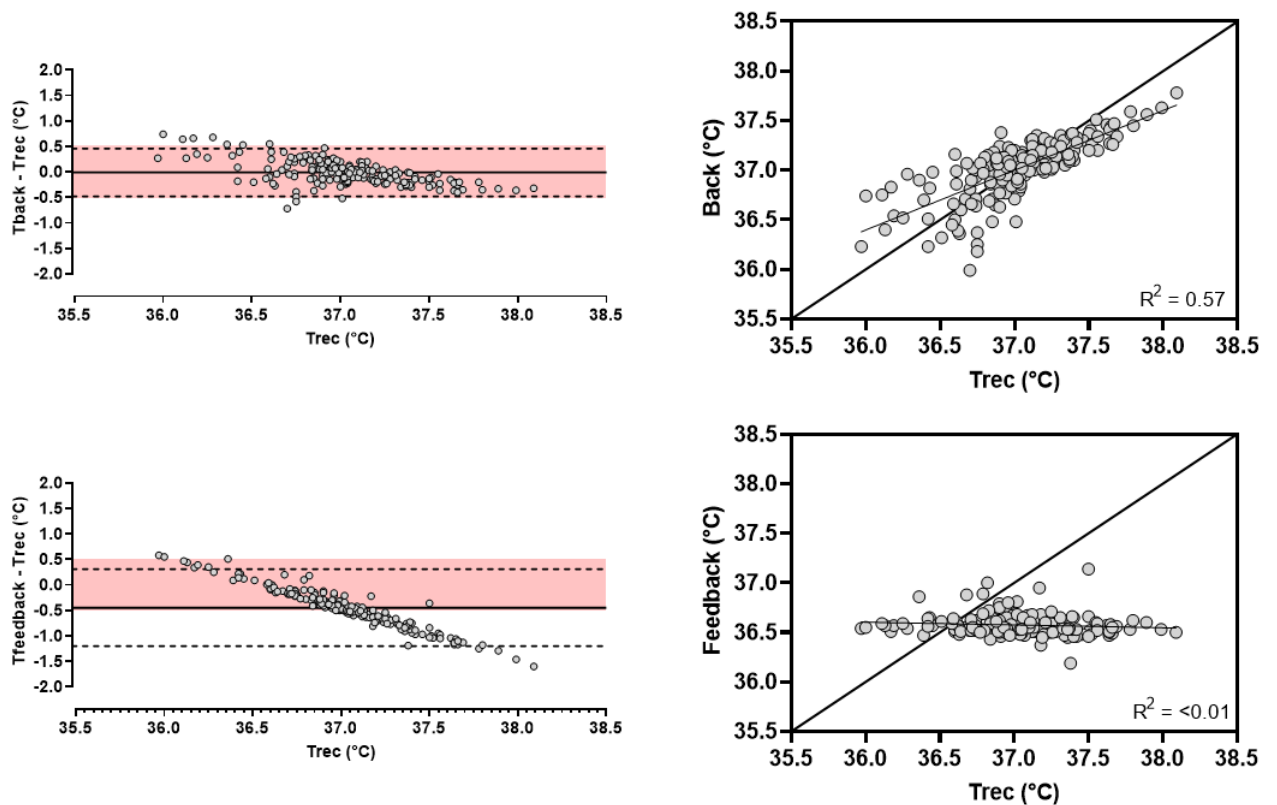


Figure 2. Left: Bland-Altman plots illustrating the mean bias (solid line) and 95% confidence intervals (± 1.96 s.d.: dotted lines) for measured rectal temperature (T_{rec}) vs the difference between rectal temperature and skin temperature measured on the back ($T_{\text{back}(\text{contact})}$) and the servo-feedback temperature sensor of the radiant warmer positioned at the mid-axillary line (in supine position). The red band indicates the *a priori* acceptable limits of agreement (± 0.5 $^{\circ}\text{C}$) for estimating core temperature. **Right:** Simple regression analysis of the relationship between $T_{\text{back}(\text{contact})}$, T_{feedback} with absolute T_{rec} in the supine position.

Prone position

The mean bias, when comparing $T_{\text{chest}(\text{contact})}$ and T_{feedback} values against T_{rec} values were $+0.02 \pm 0.19^\circ\text{C}$ (95% LoA= -0.35°C to $+0.39^\circ\text{C}$) and $-0.57 \pm 0.35^\circ\text{C}$ (95% LoA= -1.25°C to 0.11°C), respectively. Based on the acceptable limits of agreement determined a priori, 96.3% and 40.7% of $T_{\text{chest}(\text{contact})}$ and T_{feedback} values were within $\pm 0.5^\circ\text{C}$ of T_{rec} , respectively. Data pertaining to all other skin temperature sites are presented in Table 2. Figure 3 illustrates the Bland-Altman and correlation plots for $T_{\text{chest}(\text{contact})}$ and T_{feedback} relative to T_{rec} in the prone position. Due to a more limited sample size, regression analysis was not performed on data collected in the prone position.

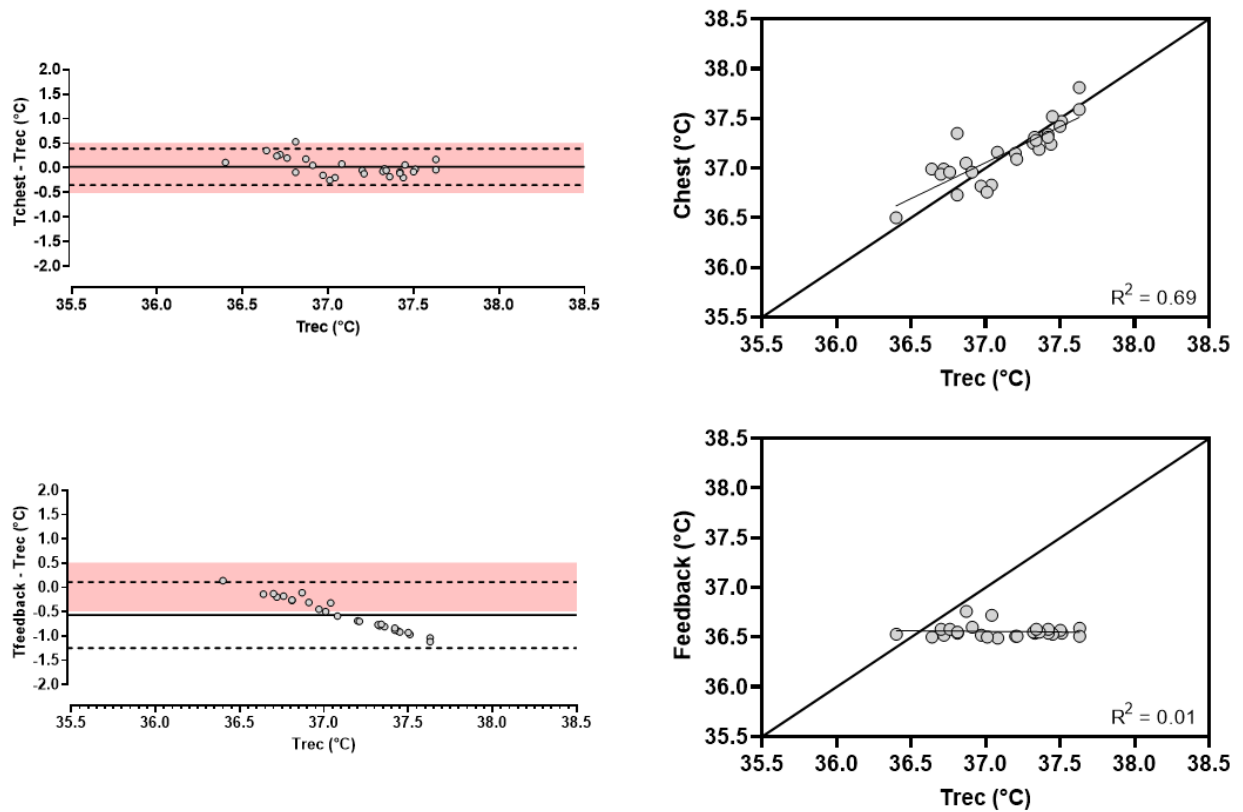


Figure 3. Left: Bland-Altman plots illustrating the mean bias (solid line) and 95% confidence intervals (± 1.96 s.d.: dotted lines) for measured rectal temperature (T_{re}) vs the difference between rectal temperature and the skin temperature measured on the chest ($T_{\text{chest}(\text{contact})}$) and the servo-feedback temperature sensor of the radiant warmer positioned at the mid-axillary line (in prone position). The red band indicates the a priori acceptable limits of agreement ($\pm 0.5^\circ\text{C}$) for estimating core temperature. Right: Simple regression analysis between absolute $T_{\text{chest}(\text{contact})}$, T_{feedback} with absolute T_{re} in the prone position.

Temporal temperature responses

Individual participant examples of the temporal $T_{\text{back}(\text{contact})}$ vs T_{rec} response are presented in Figure 4. Panels A, B and C provide examples of when infants were in the supine position throughout the observation period with the back temperature sensor in continuous contact with the incubator mattress. Panels D, E, F provide examples of when infants were periodically moved from supine to prone positions, with the back temperature sensor transitioning between mattress contact and exposure to the ambient environment.

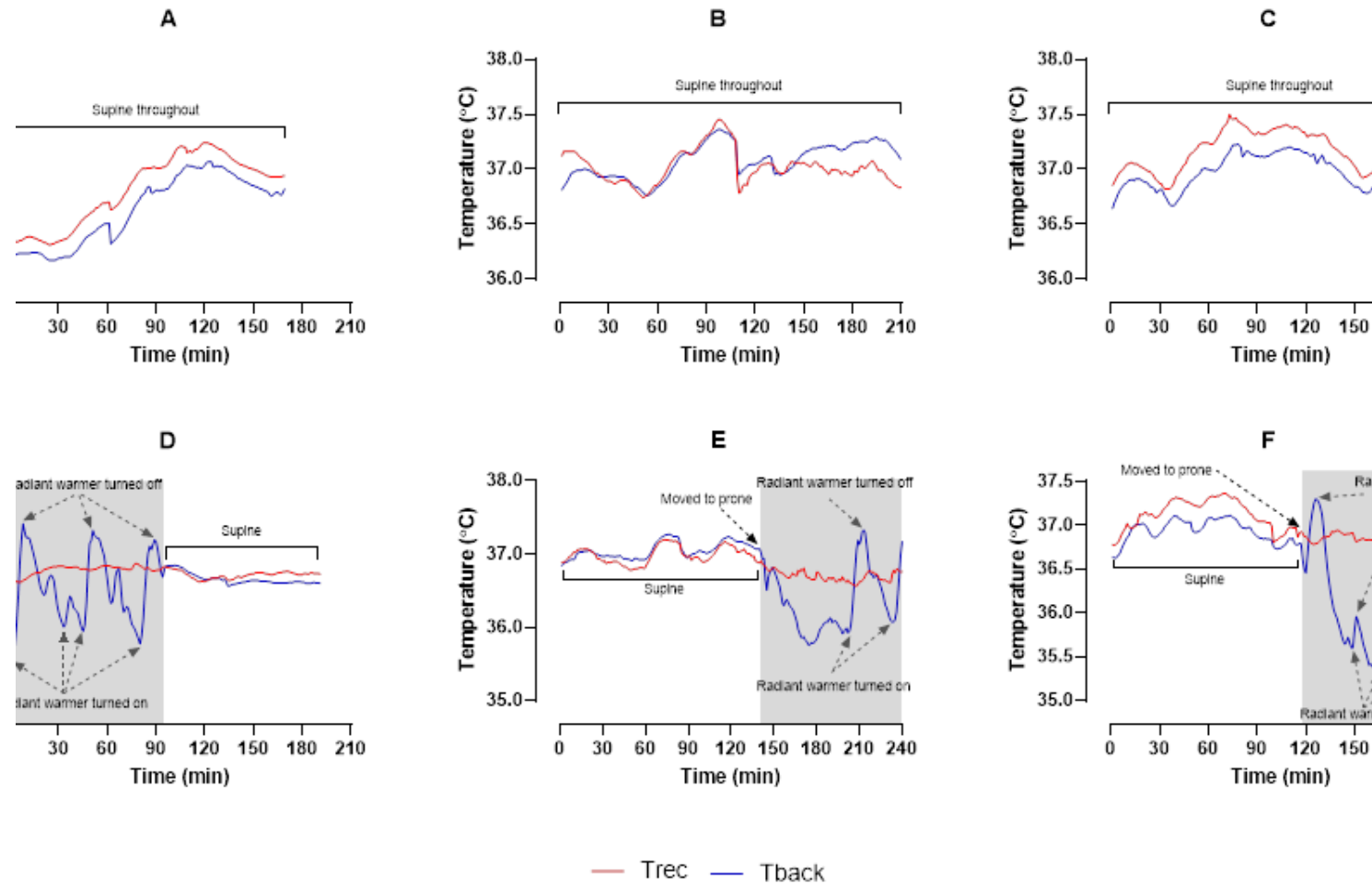


Figure 4. Individual participant examples of the temporal $T_{\text{back}(\text{contact})}$ vs T_{rec} temperature response during experimental observation. Panels A, B, C = examples of the infant in the supine position throughout testing resulting in close agreement between T_{back} and T_{rec} . Panels D, E, F = examples of discrepancies between T_{back} and T_{rec} due to either an infant position change or the radiant warmer being turned on or off.

Discussion

This study examined the suitability and level of agreement of potential skin contact temperature sites in both the supine (back temperature) and prone (chest temperature) positions as a surrogate measure of core temperature for infants nursed under an NICU radiant warmer. The level of agreement at these temperature sites, was compared to that observed for the commonly used mid-axillary servo-control temperature sensor placement (T_{feedback}). Our findings demonstrated that T_{back} provided a superior estimation of core temperature compared with T_{feedback} when the infants were nursed in the supine position and thus the sensor was insulated through direct contact with the mattress. Similarly, T_{chest} exhibited a good agreement with core temperature when the infants were nursed in the prone position. These findings highlight the potential utility of skin temperature measured at highly insulated contact sites to serve as an accurate, non-invasive surrogate measurement of core temperature in infants nursed under radiant warmers.

The close agreement of the skin contact sites (T_{back} in the supine position and T_{chest} in the prone position) with rectal temperature is explained by a phenomenon termed “zero heat flux” [22], whereby heat loss at the skin is reduced to zero due the contacting thermal insulation (e.g., warmer mattress). As a result, the temperature gradient between the temperature of the deeper tissues of the body and the skin surface is eradicated, leading to equilibration of surface and core temperatures [22, 23]. The current data clearly illustrate this occurrence. In panels A, B and C of Figure 4, skin temperature measured on the back closely tracked core temperature when infants were lying in the supine position with the back in constant contact with the mattress, with 94.9% of measurements falling within $\pm 0.5^{\circ}\text{C}$ of measured core temperature (Table 2, Figure 2). Similarly strong measurement agreement is evident in panels D, E and F of Figure 4 when the

infant was in the supine position and zero heat flux at the back was preserved. However, a clear reduction in measurement agreement was seen when the skin-to-mattress contact was disturbed when the infant transitioned from the supine position into the prone position. In such instances, substantial changes in skin temperature occurred – the direction of which was influenced by the surrounding thermal environment (e.g., the turning the radiant heater on/off). When skin-to-mattress contact was lost, the agreement between T_{back} and T_{rec} was substantially reduced and resembled that observed at other non-contact skin sites (e.g., Table 2). Albeit in a smaller dataset, the findings described above were mirrored when for T_{chest} when the infants were in the prone position with the chest instead in contact with the mattress. In contrast, the mean difference of T_{feedback} (mid-axillary) compared with core temperature was -0.45 ± 0.39 and -0.57 ± 0.35 in the supine and prone positions respectively, which is in broad agreement with previous evaluations of this measurement technique [29]. The poor agreement observed for T_{feedback} reflects the fact that mid-axillary temperature represents a surface temperature which must be lower than core temperature to enable metabolic heat to be lost at the same rate as it is produced down a temperature gradient to maintain heat balance. Additionally, whilst the temperature sensor was covered by a reflective disk to prevent direct exposure to radiant heat, the skin surface at this site was otherwise uninsulated and, therefore, liable to heat loss to the cooler ambient environment.

Previous research has advocated the use of skin contact temperature to estimate core temperature. Blackburn and colleagues [24] compared infant skin temperatures on the back and abdomen with axillary temperature and concluded that, when in contact with the mattress, these skin temperature sites likely provided a better estimation of core temperature. However, a valid measure of core temperature (e.g., oesophageal, rectal etc.) was not obtained and, therefore, the level

of agreement between estimated and measured core temperature could not be ascertained. Subsequently, it was reported that insulated temperature at the forehead yielded a mean bias of $0.19 \pm 0.53^{\circ}\text{C}$ when compared with oesophageal temperature in adults in ICU, with 92.6% of measurements falling within 0.5°C of the acceptable limits of difference [26]. Similarly, the mean difference between zero-heat-flux temperature on the forehead and oesophageal temperature was reported to be -0.23°C (LoA ± 0.82) with 78% of the differences $\leq 0.5^{\circ}\text{C}$ in adults sedated during cardiac surgery [25]. In the current study, a smaller mean bias of $-0.01 \pm 0.24^{\circ}\text{C}$ was observed for back temperature when in the supine position and $+0.02 \pm 0.19^{\circ}\text{C}$ on the chest when in the prone position, despite the infants being conscious and nursed under a radiant heater. This level of agreement also outperformed previous core temperature estimates attained from skin temperature measured over the carotid artery in anaesthetised infants [21], and the findings from Chapter 3.

From a practical clinical perspective, there are several potential advantages of using skin contact temperature measurements as a surrogate for body core temperature. First, unlike temperature measurements taken in the rectum, skin measurements are not affected by bowel movements or disturbances associated with the changing of diapers. Additionally, the external location of skin temperature sensors affords better visibility and accessibility meaning potential displacement of sensors can be easily identified and remedied. The non-invasive nature of skin contact temperature measurements may be preferable over rectal temperature when infants present with anal fissure which are common during infancy and may cause sensitivity and or obstruction in the rectum [30]. A further advantage of using a skin-contact site to obtain a temperature measurement is that, by definition, the skin thermistors are shielded by the infant's body from the heat emitted from the radiant heaters, thus preventing accidental heating of the sensors and thus

erroneous temperature measurements. Finally, due to the convenience of measurement, the use of zero heat flux skin-contact temperature to derive estimates of core temperature may be particularly suitable for long-term temperature monitoring during infant NICU stays which typically span approximately 7 days [31].

Limitations of the study include the fact that infants of a relatively narrow postnatal age range (4 to 97 days), and it is possible that the agreement between skin contact sites and core temperature may diverge with increasing age, especially as infants become more mobile, potentially compromising the integrity of the skin-to-mattress contact. Secondly, due to the nursing care requirements, the majority of data points were collected with infants in the supine position, with only 27 data points collected in the prone position. However, the data collected in the prone position closely resembled those collected in the supine position and we are confident the same zero-heat-flux effect occurred on the chest when the infant was prone. Thirdly, we acknowledge that the acceptable limit of agreement (LoA) predetermined at $\pm 0.5^{\circ}\text{C}$ will have different physiological consequences depending on the absolute core temperature, especially in the hyperthermic range, from a heat-illness perspective. However, the data demonstrated that almost 99% of all observed data points of absolute core temperature in supine (Figure 2) and 100% in the prone position (Figure 3) were less than 38°C , hence the risk of hyperthermia is minimal to zero, demonstrating that the hyperthermic range was not a cause for concern in our analysis. Finally, pulmonary arterial temperature is considered the gold-standard measurement of core temperature, however, we opted to use rectal temperature as our reference measurement due to its widespread clinical use in NICUs and its suitability for use with the population of interest [32].

Conclusion

In conclusion, our findings clearly demonstrate that skin temperature measurements when insulated through contact with a mattress – specifically the back when in the supine position and the chest when in the prone position – provide a potentially accurate and reliable representation of true deep core temperature measured in the rectum in infants nursed under a radiant warmer. Both skin-contact temperature sites examined exhibited superior agreement with rectal temperature when compared with the commonly used servo-control feedback sensor positioned along the mid-axillary line. These findings indicate that skin-contact temperature measurements may be suitable for use in clinical NICU settings to help optimise thermal care.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

The authors would like to acknowledge Chris Hargans, Senior Technical Officer (NICU, Nepean Hospital) for technical support rendered during the data collection period.

Experimental Study Two References

1. Watkinson, M., *Temperature control of premature infants in the delivery room*. Clinics in Perinatology, 2006. **33**(1): p. 43.
2. Vohra, S., et al., *Heat Loss Prevention (HeLP) in the delivery room: A randomized controlled trial of polyethylene occlusive skin wrapping in very preterm infants*. The Journal of Pediatrics, 2004. **145**(6): p. 750-753.
3. Aherne, W. and D. Hull, *Brown adipose tissue and heat production in the newborn infant*. Journal of Pathology and Bacteriology, 1966. **91**: p. 223-234.
4. Mance, M.J., *Keeping infants warm: Challenges of hypothermia*. Advances in Neonatal Care, 2008. **8**(1): p. 6-12.
5. World Health Organisation, *WHO recommendations on interventions to improve preterm birth outcomes*, W.L.C.-i.-P. Data, Editor. 2015. p. 108.
6. WHO, *Thermal Protection of the Newborn: a practical guide*. 1997, World Health Organisation: Geneva.
7. Hannenberg, A.A. and D.I. Sessler, *Improving perioperative temperature management*. Anesthesia and Analgesia, 2008. **107**(5): p. 1454-1457.
8. Laptook, A.R. and M. Watkinson, *Temperature management in the delivery room*. Seminars in Fetal and Neonatal Medicine, 2008. **13**(6): p. 383-391.
9. Narendran, V. and S.B. Hoath, *Thermal management of the low birth weight infant: A cornerstone of neonatology*. The Journal of Pediatrics, 1999. **134**(5): p. 529-531.
10. Elliott, R.I. and T.P. Mann, *Neonatal cold injury due to accidental exposure to cold*. Lancet (London, England), 1957. **272**(6962): p. 229.
11. Gandy, G.M., et al., *Thermal environment and acid-based homeostasis in human infants during the first few hours of life*. The Journal of Clinical Investigation, 1964. **43**(4): p. 751-758.

12. Pomerance, J.J., C. Madore, and L. Gluck, *Effect of temperature on survival of infants with RDS*. Pediatric Research, 1974. **8**(4): p. 449-449.
13. Lunze, K., et al., *The global burden of neonatal hypothermia: systematic review of a major challenge for newborn survival*. BMC medicine, 2013. **11**(1): p. 24-24.
14. Baumgart, S., *Iatrogenic hyperthermia and hypothermia in the neonate*. Clinics in Perinatology, 2008. **35**(1): p. 183-97, ix-x.
15. Laptook, A.R., et al., *Admission Temperature of Low Birth Weight Infants: Predictors and Associated Morbidities*. Pediatrics, 2007. **119**(3): p. e643.
16. Flenady, V. and P.G. Woodgate, *Radiant warmers versus incubators for regulating body temperature in newborn infants (review)*. Cochrane Database of Systematic Reviews, 2009(2): p. 1-41.
17. Fic, A.M., et al., *Heat and mass transfer under an infant radiant warmer--development of a numerical model*. Medical Engineering and Physics, 2010. **32**(5): p. 497-504.
18. Bell, E.F., *Infant incubators and radiant warmers*. Early Human Development, 1983. **8**(3): p. 351-375.
19. Molgat-Seon, Y., et al., *Accidental overheating of a newborn under an infant radiant warmer: a lesson for future use*. Journal of Perinatology, 2013. **33**(9): p. 738-9.
20. Chaseling, G.K., et al., *Body temperature mapping in critically ill newborn infants nursed under radiant warmers during intensive care*. Journal of Perinatology, 2016. **36**(7): p. 540-3.
21. Jay, O., et al., *Skin temperature over the carotid artery provides an accurate noninvasive estimation of core temperature in infants and young children during general anesthesia*. Paediatric Anaesthesia, 2013. **23**(12): p. 1109-16.
22. Fox, R.H., et al., *A New Method for Monitoring Deep Body Temperature from the Skin Surface*. Clinical Science and Molecular Medicine, 1973. **44**(1): p. 81-86.

23. Yamakage, M. and A. Namiki, *Deep temperature monitoring using a zero-heat-flow method*. Journal of Anesthesia, 2003. **17**: p. 108-115.
24. Blackburn, S., et al., *Neonatal thermal care, part III: The effect of infant position and temperature probe placement*. Neonatal Network 2001. **20**(3): p. 25-30.
25. Eshraghi, Y., et al., *An Evaluation of a Zero-Heat-Flux Cutaneous Thermometer in Cardiac Surgical Patients*. Anesthesia and Analgesia, 2014. **119**: p. 543-9.
26. Dahyot-Fizelier, C., et al., *Accuracy of Zero-Heat-Flux Cutaneous Temperature in Intensive Care Adults*. Critical Care Medicine, 2017. **45**: p. e715–e717.
27. Klein, A.D. and R.E. Scammon, *The regional growth in surface area of the human body in prenatal life*. Experimental Biology and Medicine, 1930. **27**: p. 463-466.
28. Kimberger, O., et al., *Accuracy and precision of a novel non-invasive core thermometer*. British Journal of Anaesthesia, 2009. **103**(2): p. 226-31.
29. Del Bene, V., *Temperature*, in *Clinical Methods: The History, Physical, and Laboratory Examinations.*, H.W.D. Walker H.K., Hurst J.W., Editor. 1990, Butterworths: Boston.
30. Lambe, G.F., et al., *Fissurectomy as a treatment for anal fissures in children*. Ann R Coll Surg Engl, 2000. **82**(4): p. 254-7.
31. Sahiledengle, B., et al., *Which Factors Predict Hospital Length-of-Stay for Children Admitted to the Neonatal Intensive Care Unit and Pediatric Ward? A Hospital-Based Prospective Study*. Glob Pediatr Health, 2020. **7**: p. 2333794x20968715.
32. O'Grady, N.P., et al., *Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America*. 2008. **36**(4): p. 1330-1349.

CHAPTER 6: BRIDGING STATEMENT

The previous two experimental studies demonstrated that alternative skin sites can be used in infants as a surrogate measure of invasive core (rectal) temperature, when nursed under an open radiant warmer in the NICU. Once these infants are clinically stable and well, they will be discharged from the hospital setting, transitioning from the indoor NICU to free-living environments at home. This shift from a tightly controlled indoor environment, to much more variable environments encountered during everyday life can pose further thermoregulatory challenges to an infant.

For example, one prevalent method of transporting infants when outdoors is via the use of a stroller. The stroller, with the infant securely strapped inside, is deemed a safe, comfortable, and practical transportation device [1]. However, during times of hot weather, the stroller is a setting in which infants may be particularly exposed to high levels of heat stress. Previous anecdotal evidence, often reported in mainstream media indicates that the temperature inside a stroller carriage can often exceed the ambient temperature, especially when exposed to high levels of solar radiation [2-6]. Furthermore, the heating of the stroller may be further exacerbated by the common parental practice of draping a dry material covering (often muslin) over the stroller carriage to shade the infant. This is concerning as exposure to heat stress inside the stroller may increase the risk for infant hyperthermia and the subsequent development of heat-related illness (e.g., dehydration, seizures) and, in extreme instances, infant death. However, there is a dearth of empirical evidence examining this in the scientific literature. Furthermore, there are no evidenced-based methods for keeping a stroller cool in hot weather. Previous research has indicated that evaporative cooling methods and fan use are effective cooling techniques for adults [7-8], however, the efficacy of these cooling strategies has not been studied in infant populations. The experimental study that will be discussed in the following chapter attempts to address this gap in the literature by investigating low-cost, and accessible cooling solutions for stroller use in hot weather.

Bridging Statement References

1. Sehat, A.R., U. Nirmal, and Z. Jin, *State of the art baby strollers: Design review and the innovations of an ergonomic baby stroller*. Cogent Engineering, 2017. **4**(1).
2. McKimmie, M. *Babies at risk from covered prams* 2012; Available from: health.thewest.com.au/news/115/babies-at-risk-from-covered-prams.
3. Holmberg, H. *Swedes risk infants' lives by covering up prams*. . The Local SE 2014; Available from: <https://www.thelocal.se/20140711/swedes-risk-infants-lives-by-covering-up-prams>.
4. *The dangers of covering your pram*. 2022; Available from: <https://rednose.org.au/news/the-dangers-of-covering-your-pram>.
5. Payton, M. *Parents placing a blanket over baby's pram in hot weather 'put their children at risk'*. 2016; Available from: <https://www.independent.co.uk/life-style/health-and-families/health-news/uk-heat-sun-pram-stroller-parents-blanket-over-baby-pram-in-hot-weather-put-their-children-at-risk-a7145311.html>.
6. Burnie, R. and C. Howe. *Pram covers can overheat children inside, safety experts warn* 2019; Available from: <https://www.abc.net.au/news/2019-01-17/pram-covers-can-overheat-children-safety-experts-warn/10721062>.
7. Song, W., F. Wang, and C. Zhang, *Intermittent wetting clothing as a cooling strategy for body heat strain alleviation of vulnerable populations during a severe heatwave incident*. Journal of Thermal Biology, 2019. **79**: p. 33-41.
8. Cramer, M.N., et al., *Keeping older individuals cool in hot and moderately humid conditions: wetted clothing with and without an electric fan*. Journal of Applied Physiology 2020. **128**(3): p. 604-611.

CHAPTER 7: EXPERIMENTAL STUDY THREE

Optimal Low-Cost Cooling Strategies for Infant Strollers during Hot Weather

The following chapter was published in *Ergonomics* in 2023.

Bin Maideen, M.F., Jay, O., Bongers, C., Nanan, R. & Smallcombe, J.W. (2023). Optimal low-cost cooling strategies for infant strollers during hot weather, *Ergonomics*. DOI: 10.1080/00140139.2023.2172212

Author contributions: MFBM, OJ, CB and RN conceived and designed experiments; MFBM performed experiments; MFBM and JS analysed data; MFBM, JS and OJ interpreted data; MFBM and JS drafted manuscript; MFBM, JS and OJ edited/revised manuscript; MFBM, OJ, CB, RN and JS approved final draft of manuscript (Appendix C).

Introduction

During periods of hot weather, the potential for infant hyperthermia is of particular concern as this can lead to adverse clinical symptoms including hypotension, dehydration, seizures and, in severe cases, infant fatality [1, 2]. Heat stress has also been linked with sudden infant death syndrome (SIDS) [3, 4] which is the leading cause of post-neonatal unexplained deaths worldwide [5]. These safety concerns are particularly salient given a limited thermoregulatory capacity during infancy, owing largely to unique morphological and physiological characteristics (e.g., higher body surface area to mass ratio, more limited sweating capacity) which may render infants liable to hyperthermia if exposed to high ambient temperatures for prolonged periods [6, 7]. Furthermore, infants are highly dependent on their adult caregivers to ensure dangerous hyperthermia is avoided through appropriate behavioural intervention such as the removal of excess clothing, avoidance of radiant heat sources (e.g., solar radiation) and the seeking of cool shelter. Ensuring caregivers are provided with evidenced- based knowledge and guidance has been identified as being crucial to improving a wide range of health out- comes during childhood [8].

On a day-to-day basis, exposure to environmental heat stress is not always avoidable during infancy, especially when caregivers engage in outdoor active travel or recreational activity. Indeed, outdoor physical activity is widely encouraged during the weeks and months after pregnancy due to both perceived and well-established benefits conferred to both mother and her young child [9, 10]. During such activities, it is common practice for infants to be transported in strollers (push- chairs) [11] during which they can be exposed to significant levels of heat stress during hot summer weather. By design, strollers are typically semi-enclosed carriages built to facilitate both structural integrity and infant comfort [12]. However, such design features may result in compromised airflow and the creation of a space prone to heat absorption and retention - all of which exacerbate the risk for infant heat

exposure.

Efforts to reduce the risk of stroller overheating have seen numerous techniques adopted by caregivers. Typically, these methods focus on reducing solar influx to the stroller carriage using material coverings e.g., muslin cloth [13] or sunshades/parasols [14] in an attempt to minimise ultraviolet (UV) radiation exposure within the stroller carriage, protecting against the long-term health consequences of UV-induced skin damage [15]. In addition, more sophisticated cooling methods such as battery-operated fans that attach to the stroller frame are also commercially available. However, despite the widespread adoption of such ‘cooling techniques’ their overall efficacy is not supported by empirical evidence and some anecdotal reports even suggest material stroller coverings may instead accelerate in-stroller heating [16, 17]. In contrast, an understanding of the basic principles of heat exchange, raises the possibility of novel low-cost stroller interventions that harness the power of evaporation. Evaporative cooling methods have been utilised effectively in other settings to help adults manage heat stress severity (e.g., misting fans [18-20], water sprays [21], moistening of clothing [22]) and may be well-suited for safe use in the context of infant stroller heat management.

Whilst thermal manikins have been used to assess infant heat stress in a range of different settings [23, 24], to the best of our knowledge no previous study has systematically examined the cooling efficacy of stroller cooling strategies, and moreover, in ecologically valid settings. Accordingly, the current study aimed to empirically examine the cooling efficacy of eight different stroller configurations; namely the stroller with: (a) the canopy closed (which served as the standard-practice control intervention); (b) a commercially available battery operated clip-on fan; (c) a white muslin cloth draped over the front of the carriage; (d) a flannelette cloth (made of polyester) draped over the front of the carriage; (e) a combination of muslin cloth and clip-on fan; (f) a combination of flannelette cloth and clip-

on fan; g) a completely moistened muslin cloth draping; and (h) a combination of a completely moistened muslin cloth draping and clip-on fan. It was hypothesised that the stroller configurations that incorporated evaporative cooling techniques would reduce the heat stress severity experienced inside the stroller carriage, whereas those that instead utilised a dry material covering would exacerbate the level of in-stroller heat stress.

Methods

All experimental trials were conducted at the University of Sydney (Cumberland campus, Lidcombe, New South Wales) between November 2019 and February 2020, during the Australian summer. No human participants were involved in this study and, therefore, human ethical approval was not required. Experimental trials were planned by consulting the Bureau of Meteorology (BOM) weather forecast based on the requirement that: (1) the peak ambient temperature was forecasted to be 30°C for at least 1h; (2) with minimal to no cloud cover; (3) and no rainfall.

A total of 16 experimental trials were conducted, each on different days. Each experimental trial consisted of the separate 20-min testing of each stroller configuration (Table 1) in a counterbalanced order. Including the set-up time and equilibration period required between each stroller configuration, each trial lasted approximately 4.5 hours. All trials commenced at 1100 h (± 30 min) and were completed by 1530 h (± 30 min).

Table 1. Summary of cooling interventions (see Figure 3 for images).

Stroller configuration	Description
<i>Stroller Closed Control</i>	Stroller with the canopy in a propped-down position (standard practice control intervention)
<i>Fan Only</i>	Battery-operated clip-on fan attached to the centre of the bumper bar (~60cm away from the likely position of the infant), directing wind inwards to the stroller carriage
<i>Muslin Only</i>	Muslin (100% cotton) covering draped over propped-down canopy covering the front of stroller – secured to stroller with clothes pegs
<i>Flannelette Only</i>	Dry flannelette (100% polyester) covering draped over the propped-down canopy covering the front of stroller – secured to stroller with pegs
<i>Muslin + Fan</i>	As per <i>Muslin Only</i> , with a clip-on fan attached to the centre of bumper bar beneath muslin covering
<i>Flannelette + Fan</i>	As per <i>Flannelette Only</i> , with the clip-on fan attached to the centre of bumper bar beneath flannelette covering
<i>Muslin + Moist</i>	As per <i>Muslin Only</i> , with the muslin cloth thoroughly soaked in tap water and wrung (non-dripping) prior to draping
<i>Muslin + Fan + Moist</i>	As per <i>Muslin + Moist</i> , with clip-on fan attached to the centre of bumper bar beneath moistened muslin covering

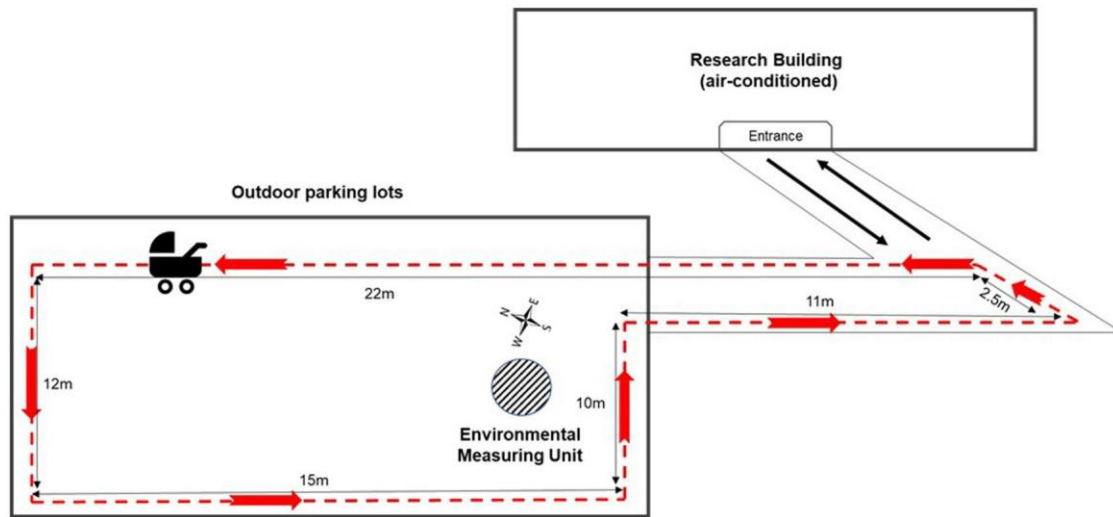


Figure 1. Schematic diagram of pre-determined 72.5 m route along which the stroller was pushed during each 20-min intervention. The red dashed lines indicate the stroller route, the red arrows indicate the direction, the hatched circle indicates the location of the environmental measuring unit, placed on the tarmac of the nearby parking lot unobstructed.

A standard infant stroller (Inglesina Trilogy stroller, Italy) made with a lightweight and waterproof polyester canvas material with full-recline backrest, full-pivoting canopy and a removable bumper bar was used for all trials. The stroller in its unfolded position presented with the dimensions of 56 cm (width), 105.5 cm (height) and 82 cm (depth), with a weight of 9.6 kg. This stroller design was selected for testing as it was commercially available and deemed to be broadly ‘typical’ in dimension and material composition. Future research is warranted to examine if the current findings are generalisable to other stroller models with different design features. It should be noted that the cooling interventions tested in the current study were selected as they could be feasibly used in conjunction with most standard stroller designs. During all trials, the stroller was pushed by the same researcher at a comfortable walking speed (approximately 1.4 m/s) along a predetermined 72.5m outdoor route (see Figure 1). The set-up of the stroller between configurations was conducted in an adjacent air-conditioned room (temperature of $23 \pm 1^\circ\text{C}$; relative humidity of $70 \pm 5\%$) over the course of 10-min to ensure the baseline in-stroller temperature conditions were consistent between configurations.

Instrumentation

Temperature sensors

A purpose-built wire frame was fitted into the internal stroller carriage to which six temperature sensors (YSI409B with 9.5 mm sensor, range of operation: 0–60°C; accuracy: $\pm 0.2^\circ\text{C}$ from 0°C to 60°C, $\pm 0.1^\circ\text{C}$ from 25°C to 45°C) were suspended to measure air temperature. These temperature sensors were shielded from direct solar radiation by the stroller canopy (which was closed) or the stroller canopy and the cloth covering in combination. Four thermistors were positioned to simulate the location of body segments of an infant (i.e., head, chest, abdomen, and lower limbs); and two thermistors were suspended 15 cm from the top of the canopy to provide an indication of the thermal conditions in the upper portion of the stroller carriage space (Figure 2). All thermometric measurements were sampled at 5-s intervals via a portable data acquisition box and displayed in real-time via a laptop using LabView software (v7.0. National Instruments, Austin, TX), for a total duration of 20 min per intervention.

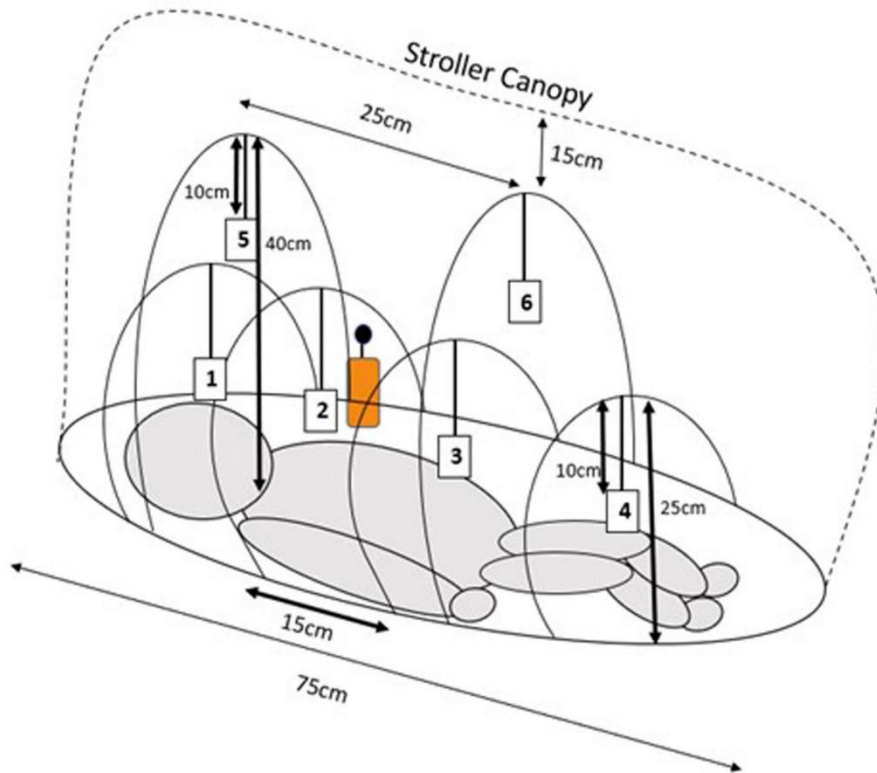


Figure 2. In-stroller thermistors and Kestrel 5400-unit placement within the purpose-built wire frame. Numbers 1–4 indicate individual thermistor placement relative to a simulated infant’s body segments (i.e., head, chest, abdomen, and legs). Numbers 5 and 6 indicate the thermistor placement measuring the temperature in the upper portion of the stroller carriage space, close to the canopy. The orange icon indicates the location of the Kestrel 5400 unit, placed near the centre of the wire frame, which was suspended 15 cm above the stroller seat surface.

Other in-stroller environmental parameters

A Kestrel 5400 series (Nielsen-Kellerman, Pennsylvania, PA) portable unit was also positioned in the stroller to measure in-stroller air temperature (T_a), relative humidity (RH), natural wet bulb temperature (T_{nwb}), black globe temperature (T_{globe}), wet bulb globe temperature (WBGT) and air velocity. WBGT was calculated using the following equation: $WBGT = 0.7T_{wb} + 0.2T_{globe} + 0.1T_{db}$. The unit was placed in the centre of the stroller carriage in an upright position (Figure 2) and was secured 15 cm above the stroller seat surface by the purpose-built wire frame. All measurements were sampled at 5-second intervals.

External environmental parameters

Outdoor air temperature, relative humidity, wind speed, and black globe temperature were measured by an environmental measuring unit (EMU) designed and built by the University of Sydney. Wind speed and direction were measured using an ultrasonic anemometer (Gill Instruments, UK). Black globe temperature was measured using a 100 mm platinum resistance thermometer (Temperature Controls, Australia) placed inside a 150 mm diameter copper globe (Irrigation Direct, Australia) painted matt black. Air temperature and wet bulb temperature were measured using two 100 mm platinum resistance thermometers (Temperature Controls, Australia). Both thermometers were mechanically aspirated with one covered with a cotton shroud and saturated with distilled water. A temperature data logger unit (Pico Technology PT-104, RS Components, Australia) with an accompanying PicoLog 6 application programming software was used to record temperature measurements. The instruments were mounted on a modified tripod stand (Jaycar, Australia) at a height of 1.2 m. During all trials, the EMU was placed at a standardised, unobstructed location along the pre-determined route (see Figure 1). All environmental measurements were sampled and recorded at 5-s intervals via a tablet (Microsoft Surface Go) using customised software with the data subsequently exported for analysis.

Stroller configurations

The eight stroller configurations tested in the study were selected due to their conventional day-to-day use, using inexpensive and readily available resources (see Table 1, Figure 3). In the *Closed Stroller* configuration, the stroller canopy was put down, shading the stroller carriage from solar radiation whilst not impeding the airflow through the carriage (Figure 3). We opted for this control configuration as we deemed it likely that caregivers would opt to close the canopy during hot weather to help avoid excessive UV exposure.



Figure 3. The tested stroller cooling interventions. All fabric drapings were secured using plastic clothes pegs, ensuring that there were no gaps present. For illustrative purposes, the drapings of interventions E and F were raised on one side to display the position of the battery-operated fan.

During the configurations involving the clip-on battery-operated fan (Tee-Zed Products, Guangdong, China), new batteries were used for each trial to avoid decrements in maximal fan speed, which was confirmed before each trial to be approximately 1 m/s. Muslin coverings (112 cm by 112 cm) which were predominantly white in colour and made from 100% cotton weave were used due to its high capacity to absorb moisture. One dry muslin covering was used for both the *Muslin Only* and *Muslin + Fan* trials. Two separate muslin coverings, which were saturated with tap water, were used for the *Muslin + Moist* intervention, and the *Muslin + Fan + Moist* intervention. The flannelette covering (112 cm by 112 cm), made from 100% polyester, was not moistened as it was a non-absorbent material. Both the muslin and flannelette coverings were draped over the stroller carriage as single layer (i.e., unfolded).

Experimental protocol

Before the start of experimentation, three muslin covering were prepared for use. Two of these muslin coverings were weighed with a digital scale ($\pm 0.1\text{g}$, Mettler Toledo, MS12001L) before and after being soaked in room temperature tap water and wrung-out to ensure complete saturation but to avoid dripping. These wet muslin coverings were then stored in separate sealed plastic bags until use to prevent water loss via evaporation.

The set-up of each stroller configuration was conducted in an air-conditioned room set to 23°C. The stroller backrest was placed in a full recline (supine) position to simulate a young infant's (from birth to 6 months) typical positioning.

Based on the counterbalanced order, one of the eight stroller configurations was assigned as the first to be tested and the stroller was prepared accordingly. Before the prepared stroller was taken out of the air-conditioned room, a five-minute baseline period was observed to ensure that all stroller temperature sensors had equilibrated to room temperature (within 1°C), across all temperature sensors. The stroller was then pushed continually outdoors along the pre-determined route (see Figure 1) at a comfortable walking speed of approximately 1.4

m/s. Each stroller configuration was tested for 20 minutes, at which point the stroller was pushed back to the air-conditioned room and placed in front of a pedestal fan to cool the interior carriage of the stroller to baseline room temperature. Once cooled, the stroller was prepared for the next experimental intervention. This process was repeated eight times each experimental day until all stroller configurations had been tested (Table 1).

Statistical analysis

All data are reported as means with standard deviation, unless otherwise stated. The GraphPad Prism (version 8.3.0, GraphPad Software, La Jolla, CA) software was used for all data analyses. Environmental parameter data for each stroller configuration were averaged over the 16 days of experimental testing. Separate one-way repeated measures ANOVA with the independent variable of stroller configuration (eight levels: *Stroller Closed*; *Fan Only*; *Muslin Only*; *Flannelette Only*; *Muslin and Fan*; *Flannelette and Fan*; *Muslin + Moist*; *Muslin + Fan + Moist*) were used to analyse the differences in dependent variables (mean and end-of-trial environmental parameters). Paired T-tests were used to compare the volume of water evaporated, rate of water evaporation and the heat liberated from the evaporation of water from the muslin cloths. An alpha of 0.05 was used to determine statistical significance, hence, the probability of making type 1 error in all tests was maintained at 5%. When a significant effect was found, planned pairwise comparisons were made against the *Closed Stroller Control* configuration using two-tailed paired-samples t-tests, with Bonferroni adjustments made for multiple comparisons.

Results

Outdoor environmental conditions

The average outdoor air temperature ($p = 0.257$), relative humidity ($p = 0.224$), black globe temperature ($p = 0.388$), air velocity ($0.89 \pm 0.33 \text{ ms}^{-1}$, $p = 0.135$), and WBGT ($p = 0.598$) did not differ across the testing of the eight stroller configurations. The end-trial outdoor environmental parameters for each stroller configuration are presented in Table 2.

In-stroller environmental conditions

The average temporal (minute averaged) in-stroller environmental conditions for each stroller configuration are displayed in Figure 4.

End-trial absolute stroller temperatures

An effect of stroller configuration was observed for absolute in-stroller air temperature ($p < 0.001$), relative humidity ($p < 0.001$), black globe temperature ($p < 0.001$) and WBGT ($p < 0.001$). These data are presented in Table 2. In summary, the lowest absolute in-stroller air temperature was observed in *Muslin + Moist + Fan* ($32.3 \pm 4.2^\circ\text{C}$) followed by *Muslin + Moist* ($33.6 \pm 5.1^\circ\text{C}$), both of which were significantly lower than *Closed Stroller Control* ($37.5 \pm 4.7^\circ\text{C}$) ($p < 0.009$). In contrast, the highest absolute in-stroller air temperature was observed in *Flannelette Only* ($40.0 \pm 4.8^\circ\text{C}$), followed by the *Flannelette + Fan* ($39.5 \pm 4.2^\circ\text{C}$) and *Muslin Only* ($39.2 \pm 4.5^\circ\text{C}$) configurations, all of which were higher than the *Closed Stroller Control* ($p < 0.026$). No differences in absolute in-stroller air temperature were observed in the *Fan Only* ($37.2 \pm 4.8^\circ\text{C}$) or the *Muslin + Fan* ($37.9 \pm 3.3^\circ\text{C}$) configurations compared with the reference control configuration ($p > 0.995$).

Table 2. The mean (mean of 16 separate experimental observations) end of trial in-stroller and outside ambient environmental conditions and the mean differences observed between in-stroller vs outside for each stroller configuration.

Stroller configuration	Outside Air Temp (°C)	In-stroller Air Temp (°C)	Outside absolute humidity (mmHg)	In-stroller absolute humidity (mmHg)	Outside Relative Humidity (%)	In-stroller Relative Humidity (%)	Outside Black Globe (°C)	In-stroller Black Globe (°C)	Outside WBGT (°C)	In-stroller WBGT (°C)
<i>Closed-Stroller (Control)</i>	34.0 ± 4.3	37.5 ± 4.7	13.5 ± 5.2	16.4 ± 5.0	34.7 ± 14.4	34.6 ± 11.8	44.1 ± 4.7	40.4 ± 4.2	27.6 ± 3.4	28.3 ± 3.4
<i>Fan Only</i>	33.8 ± 4.6	37.2 ± 4.8	13.6 ± 5.3	16.5 ± 5.6	35.1 ± 14.9	35.0 ± 12.3	44.4 ± 5.1	38.8 ± 4.6	27.6 ± 3.6	27.7 ± 3.6
<i>Muslin Only</i>	33.1 ± 4.2	39.2 ± 4.5 [†]	13.9 ± 5.2	17.1 ± 5.6	37.5 ± 15.7	32.3 ± 10.7	43.5 ± 5.9	42.3 ± 5.4	27.3 ± 3.6	28.9 ± 3.6
<i>Flannelette Only</i>	32.8 ± 4.4	40.0 ± 4.8 [†]	13.8 ± 5.2	18.2 ± 6.1	38.0 ± 16.2	32.7 ± 10.7	43.5 ± 5.2	42.7 ± 4.7	27.2 ± 3.6	29.3 ± 3.5
<i>Muslin + Fan</i>	32.9 ± 3.1	37.9 ± 3.3	14.0 ± 5.0	16.4 ± 5.0	37.7 ± 14.2	33.0 ± 9.7	43.2 ± 3.9	39.7 ± 3.7	27.3 ± 3.1	28.7 ± 3.3
<i>Flannelette + Fan</i>	33.6 ± 4.0	39.5 ± 4.2 [†]	13.5 ± 5.1	16.2 ± 5.0	35.6 ± 15.2	30.6 ± 10.9	44.1 ± 4.3	40.7 ± 4.1	27.4 ± 3.0	29.3 ± 3.0 [†]
<i>Muslin + Moist</i>	33.1 ± 4.1	33.6 ± 5.1 [*]	14.2 ± 4.8	19.7 ± 5.4 [†]	38.0 ± 14.4	50.5 ± 11.3 [†]	43.6 ± 5.0	36.6 ± 4.7 [*]	27.5 ± 3.4	27.7 ± 3.4
<i>Muslin + Fan + Moist</i>	33.5 ± 3.6	32.3 ± 4.2 [*]	13.7 ± 5.1	19.9 ± 4.7 [†]	36.0 ± 14.6	55.0 ± 11.4 [†]	43.8 ± 4.1	33.2 ± 3.9 [*]	27.4 ± 3.0	26.7 ± 3.2 [*]

Δ In-stroller vs outside environmental conditions					
	Δ Air Temp (°C)	Δ Absolute Humidity (mmHg)	Δ Relative Humidity (%)	Δ Black Globe (°C)	Δ WBGT (°C)
<i>Closed-Stroller (Control)</i>	+3.5	+2.9	-0.1	-3.7	+0.7
<i>Fan Only</i>	+3.4	+2.9	-0.1	-5.6	+0.1
<i>Muslin Only</i>	+6.1	+3.2	-5.2	-1.2	+1.6
<i>Flannelette Only</i>	+7.2	+4.4	-5.3	-0.8	+2.1
<i>Muslin + Fan</i>	+5.0	+2.4	-4.7	-3.5	+1.4
<i>Flannelette + Fan</i>	+5.9	+2.7	-5.0	-3.4	+1.9
<i>Muslin + Moist</i>	+0.5	+5.6	+12.5	-7.0	+0.2
<i>Muslin + Fan + Moist</i>	-1.2	+6.3	+19.0	-10.6	-0.7

* Significantly lower than Closed Stroller Control (P<0.05). † Significantly higher than Closed Stroller Control (P<0.05).

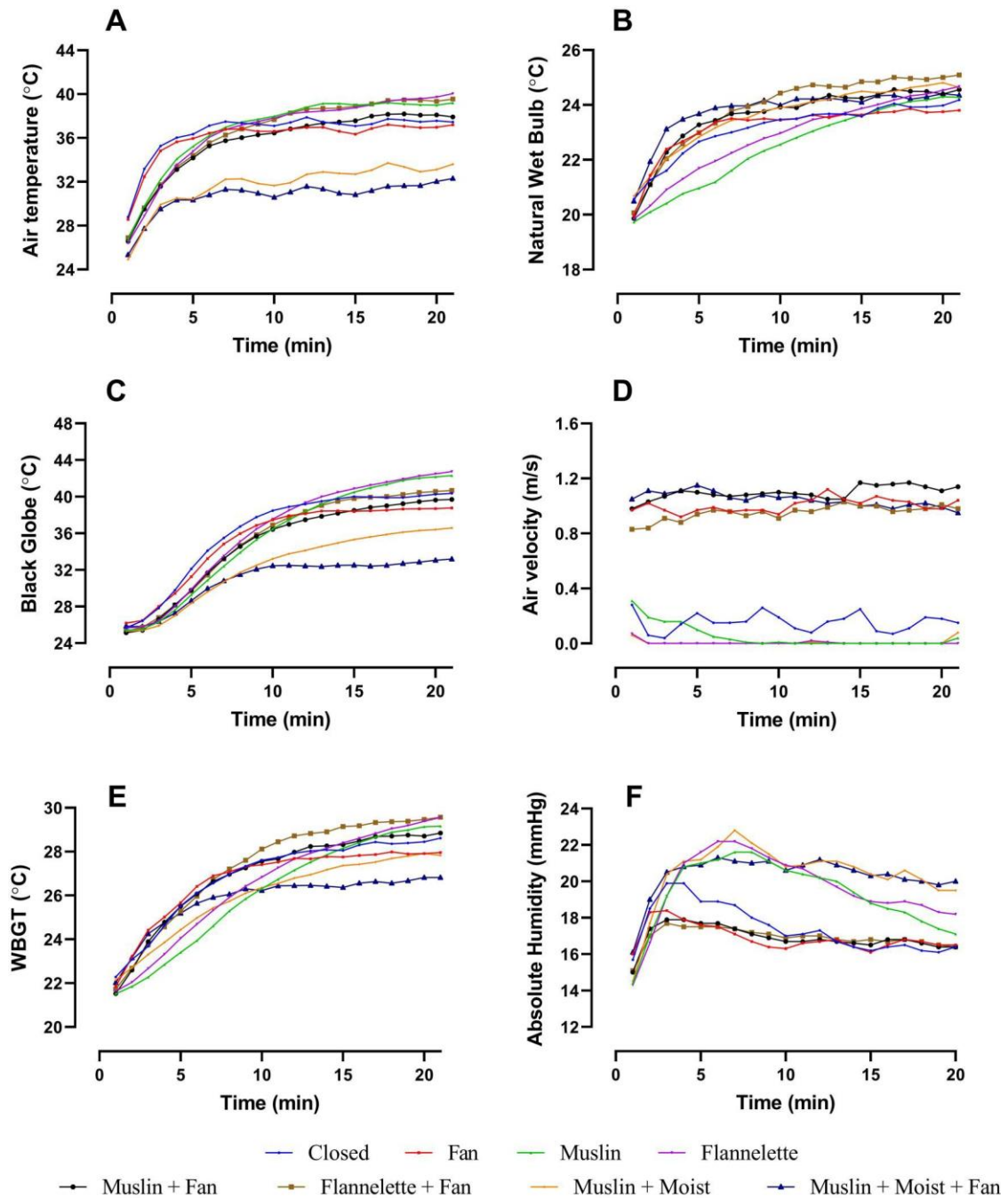


Figure 4. The mean (minute averaged data) in-stroller environmental conditions for each stroller cooling intervention. Due to the number of interventions presented, error bars have been omitted for clarity.

The lowest absolute in-stroller WBGT was also observed in *Muslin + Moist + Fan* ($26.7 \pm 3.2^{\circ}\text{C}$) which was lower than the *Closed Stroller Control* ($28.3 \pm 3.4^{\circ}\text{C}$) ($p = 0.009$). In contrast, the highest absolute WBGT was observed in *Flannelette Only* ($29.3 \pm 3.5^{\circ}\text{C}$) which

was higher than the *Closed Stroller Control* configuration ($p = 0.024$). The in-stroller absolute WBGT did not differ in any other stroller configuration when compared with *Closed Stroller Control* ($p > 0.072$).

In-stroller vs outside temperatures

The differences between the end-trial internal stroller temperatures and the corresponding outside temperatures are presented in Table 2, with an effect of stroller configuration observed for all environmental parameters ($p < 0.001$). In *Closed Stroller Control* the internal stroller air temperature was 3.5°C higher than outside ($p < 0.0001$), whilst WBGT was 0.7°C higher ($p = 0.0016$). In comparison, during *Muslin + Moist + Fan* the in-stroller air temperature did not differ to outside ($p = 0.124$), however, the internal WBGT was lower than outside ($p < 0.0001$). During *Muslin + Moist* neither the in-stroller air temperature ($p = 0.445$) or WBGT ($p = 0.446$) differed to outside. During *Fan Only*, the air temperature was higher than outside ($p < 0.0001$), but the in-stroller WBGT did not differ ($p = 0.796$). All other stroller configurations resulted in a significantly higher in-stroller air temperature and WBGT compared with outside ($p < 0.001$).

Difference between in-stroller vs outside temperatures relative to Closed-Stroller control

When the differences in in-stroller vs. outside temperatures observed in the *Closed Stroller Control* (i.e., air temperature: +3.5°C, WBGT: +0.7°C) are used anchors for comparison, the relative efficacy of the other stroller configurations in lowering the internal stroller temperatures are presented in Figure 5.

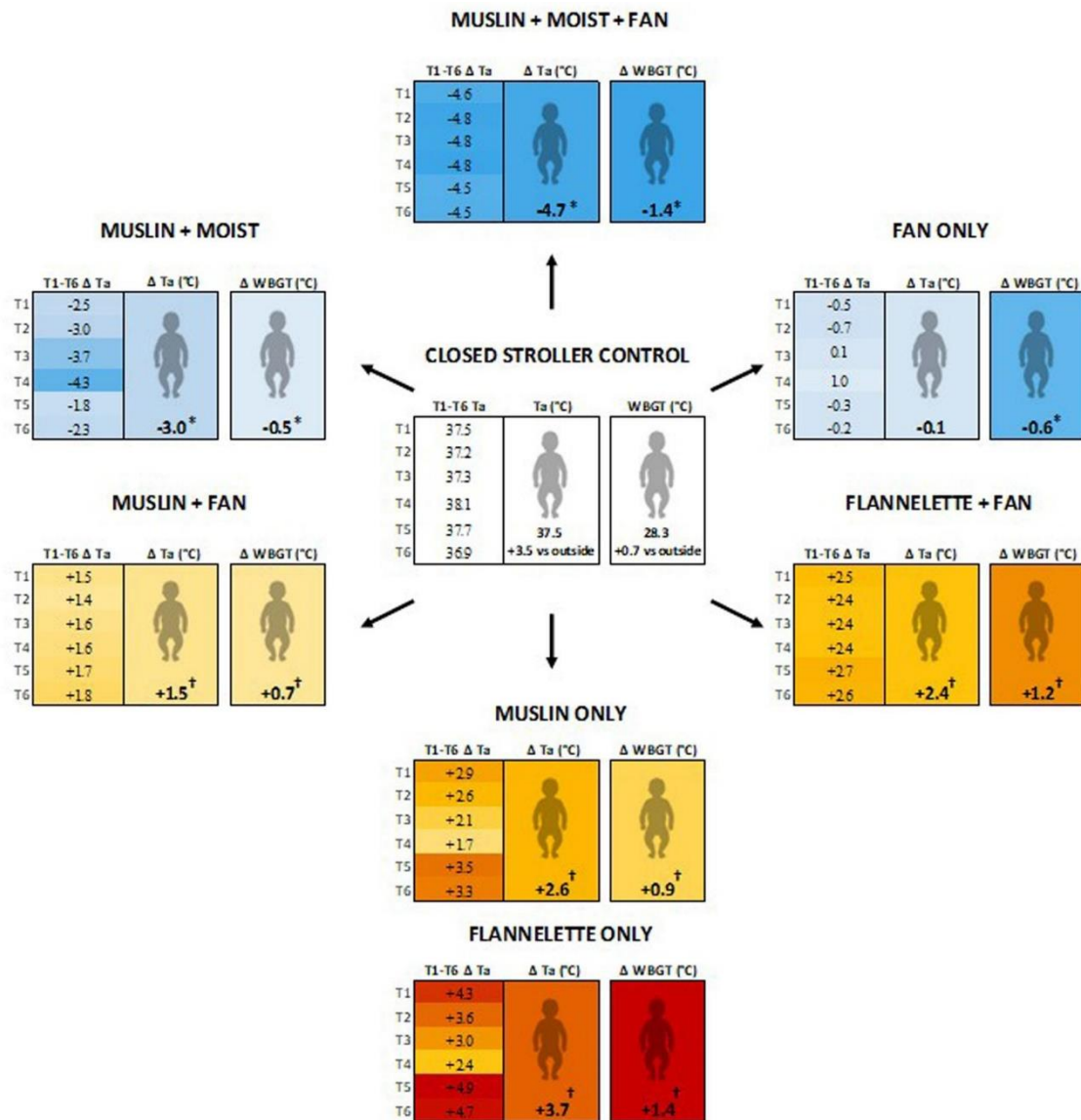


Figure 5. The mean end-trial difference between the in-stroller vs outside air temperature (T_a) and WBGT, expressed relative to the difference observed during *Closed Stroller Control*. T1–T6 represent the mean relative ΔT_a for each of the six thermistors located in the stroller chamber. *Significantly lower than *Closed Stroller Control* ($p < 0.05$). †Significantly higher than *Closed Stroller Control* ($p < 0.05$).

Table 3. Muslin characteristics pre- and post-trial and the evaporative cooling yielded.

	Muslin + Moist	Muslin + Moist + Fan	P
Dry mass muslin Pre (g)	171± 6	170 ± 7	0.720
Wet mass muslin Pre (g)	601 ± 52	577 ± 55	0.302
Wet mass muslin Post (g)	437 ± 73	391 ± 67	0.037*
Water evaporated (g)	164 ± 36	186 ± 50	0.011*
Heat liberated (kJ)	399 ±86	452 ±121	0.011*
Rate of evaporation (g/min)	8.2 ± 1.8	9.3 ± 2.5	0.011*
Water remaining (g)	266 ± 74	220 ± 68	0.042*

Relative to *Closed Stroller Control*, the greatest reduction in air temperature ($p < 0.0001$) and WBGT ($p = 0.0004$) was observed in *Muslin + Moist + Fan*. Smaller -but still significant - reductions in air temperature ($p = 0.009$) and WBGT ($p = 0.015$) were observed in *Muslin + Moist*, compared with the *Closed Stroller Control* reference condition. During the *Fan Only* configuration the in-stroller vs outside difference did not differ for air temperature relative to the *Closed Stroller Control* ($p = 0.999$) but a larger reduction in WBGT was observed ($p = 0.033$).

All other stroller configurations resulted in a larger elevation of in-stroller air temperature and WBGT compared with the *Closed Stroller Control* ($p < 0.032$). The most severe heating effect was observed in *Flannelette Only* followed by *Muslin Only*. Smaller -but still substantial - increases in in-stroller temperatures were observed in the *Muslin + Fan* and *Flannelette + Fan* configurations.

Water evaporation from moistened cloths

The mass of the muslin and flannelette cloths before and after water saturation and pre and post each experimental trial are presented in Table 3. The values were used to derive the

amount of water evaporated from the cloth and the resultant heat liberation during each trial (i.e., water evaporation (g) = wet mass muslin Pre (g) – wet mass muslin Post (g)). The heat liberated by the evaporation of water from the wet muslin cloths was calculated assuming a latent heat of water evaporation of 2430 J/g at 30°C.

Discussion

The present study examined the efficacy of eight low-cost stroller configurations commonly adopted during hot and moderately humid summer weather to mitigate the development of in-stroller carriage heat stress. The main findings of the study are: (1) draping a light-coloured moist muslin cloth over the stroller carriage reduced both the air temperature and the WBGT inside the carriage; (2) this stroller configuration was further optimised when coupled with the use of a clip-on battery operated fan; (3) the use of clip-on fan in isolation yielded a marginal reduction in WBGT, but had no effect on air temperature; (4) all other configurations - including the draping of dry muslin and flannelette cloths over the stroller carriage - worsened the prevailing level of heat stress inside the stroller.

Stroller cooling: harnessing evaporation

The largest cooling effects were observed when a moist muslin cloth was draped over front of the stroller. This cooling effect can be attributed to the evaporation of moisture from the cloth resulting in the extraction of latent heat energy from the stroller carriage. When a moist muslin draping was used in isolation (*Muslin + Moist*) in-stroller air temperature was reduced by 3.0 °C compared with the standard- practice *Closed Stroller* control configuration (Figure 5). Additionally, a 0.5°C reduction in WBGT - a unified heat index which integrates the key parameters of the thermal environment to determine the overall heat stress severity - was also observed inside the stroller when covered with a moist muslin cloth.

The moist muslin draping provided an even larger cooling effect when combined with a battery-operated fan attached to the front of the stroller which circulated air around the stroller carriage at approximately 1 m/s (*Muslin + Moist + Fan*). The additional forced convection contributed to increased water evaporation from the cloth (approximately 22g, Table 3), further augmenting heat loss from the stroller, whilst also reducing the vertical temperature gradient

evident throughout the carriage (Figure 5). This combined intervention, reduced in-stroller air temperature by 4.7°C and the WBGT by 1.4°C, compared with the *Closed Stroller Control*. It should, however, be noted that whilst air temperature and WBGT were lowered by the wet drapings, the water vapour pressure (absolute humidity) inside the stroller was increased in the stroller carriage (Figure 4, Table 2), which may have implications for in-stroller thermal comfort.

Evaporative cooling techniques have been reported previously to be efficacious in an array of different contexts for adults exposed to heat stress, including via misting fans [18-20], water dousing [21] and the moistening of clothing garments [22]. Whilst it is important to acknowledge that the evaporative cooling techniques examined in the current study may be less effective in hot and very humid conditions owing to a lower evaporative potential of the environment, the current findings do highlight the potential utility of evaporative cooling techniques to help safeguard infants during hot and moderately humid weather. Future research is warranted to examine the efficacy of stroller cooling techniques under different climatic conditions.

Increasing convection via a battery-operated fan

When a battery-operated fan was used in isolation (*Fan Only*), the in-stroller air temperature did not differ to the *Closed Stroller control*. Thermodynamic principles explain this observation as increasing convection via a fan provides no physical means of heat extraction and merely facilitates additional circulation of warm ambient air which is, at best, equal to the outdoor shaded air temperature. However, the higher internal air velocity did result in a small (0.6°C) reduction in WBGT, compared with the *Closed Stroller Control* configuration. Critical environmental threshold limits for electric fan efficacy have been defined previously [25-28] and indicate that fans are always beneficial when air temperature is

lower than human skin temperature, but can also confer thermoregulatory advantage at temperatures at least as high as 40°C. However, the efficacy of fan use at these higher temperatures is reliant on their facilitation of additional sweat evaporation from the skin surface. Whilst most babies >37 weeks (gestational age) can secrete sweat [29], their maximal sudomotor capacity is thought to be up to three times lower than that observed in older children and adults [30]. Additionally, the stroller setting is unique in that only half of the infant's body surface area is available for convective and/or evaporative heat exchange as the other half is obscured by the seat which may in turn alter the efficacy of fan-based cooling interventions. Given these considerations, in-stroller fans (without accompanying evaporative cooling methods) should be used with caution, and future research is required to determine the upper environmental limits for safe and effective fan use during infancy.

In-stroller thermal environment: Beware of potential heating effects

It was noteworthy that other stroller covering techniques substantially exacerbated the in-stroller heat stress compared with the *Closed Stroller* control. The draping of both dry muslin and dry flannelette cloths over the front of the stroller carriage increased the in-stroller air temperature (*Muslin Only* = +2.6°C; *Flannelette Only* = +3.7°C) and WBGT (*Muslin Only* = +0.9°C; *Flannelette Only* = +1.4°C). The covering of the stroller entrance with either a dry muslin or flannelette cloth reduced natural ventilation through the stroller - as evidenced by lower air velocity observed in the covered stroller configurations (Figure 4(d))—resulting in a net heating of the carriage as heat was gradually absorbed and retained.

To date, only anecdotal evidence of elevated in-stroller temperatures during hot weather has been reported [17]. However, more robust evidence derived from vehicle research indicates that even in moderately hot ambient conditions (e.g., 32 °C), the internal temperature of an enclosed vehicle (e.g., a car) can be up to 25 °C higher, leading to very dangerous levels of

heat stress [31, 32]. Our data highlight that a similar phenomenon could manifest when the stroller carriage is encapsulated with a dry material covering. For example, during the final 15-min of *Muslin Only* configuration the stroller carriage heated at a rate of $+0.20\text{ }^{\circ}\text{C}/\text{min}$, whilst a similar heating rate of $+0.26\text{ }^{\circ}\text{C}/\text{min}$ was observed during the *Flannelette Only* strategy. It therefore stands to reason that substantial - and potentially hazardous - elevations in carriage temperature could develop over longer heat stress exposures (e.g., 1 h).

The addition of a battery-operated fan to the dry cloth configurations did attenuate the in-stroller heating effect yet failed to provide benefit relative to the *Closed Stroller Control*. In terms of material selection, the dry flannelette draping resulted in higher end-trial stroller temperatures, compared to the dry muslin covering; an observation likely explained by the additional thickness and polyester composition of the flannelette which is associated higher thermal resistance [33, 34] which promotes additional heat retention. It should be acknowledged that the muslin and flannelette cloths were not matched exactly for colour which may have impacted the absorption, reflection, and transmission of radiant heat [35], however, both were both predominantly white in colour with a printed pattern (which was however slightly darker on the flannelette).

However, regardless of material type, our data provide compelling evidence that dry material coverings that excessively impede airflow through the carriage should not be used to cover the stroller during periods of hot weather. One important caveat here is that whilst refraining from fully covering the stroller carriage with a material draping, it is important that efforts are taken to ensure the carriage is not directly exposed to solar radiation. For example, this may be achieved by closing the stroller canopy - as was the case in the *Closed Stroller* control configuration - or by other means such as the use of a parasol attached to the stroller frame which may serve to provide shade without impeding airflow through the stroller carriage.

Physiological relevance

Although the physiological consequences of the differing stroller configurations were not assessed, the thermo-physiological relevance of our findings is clear. Whilst wide variations in sweating responses are observed among infants depending on their age and maturation status [36], their absolute sweating capacity can be up to three-times lower than that of adults [30, 37]. Although this impairment may be negated to a certain extent by a greater sweat output per unit of body mass due to a higher surface area-to-body mass ratio, it is generally accepted that infants exhibit a lower capacity to dissipate body heat via evaporative pathways compared with older children and adults [2, 6]. Additionally, their surface area-to-mass ratio may also promote dry heat gain when ambient temperature exceeds skin temperature, further increasing the risk for infant hyperthermia. This is particularly salient as babies/infants typically exhibit lower skin temperatures compared with older children and adults [38] meaning that the skin-to-ambient temperature gradient is reversed in favour of heat storage (skin temperature < ambient temperature) at lower ambient temperatures. It is also desirable to limit the severity of heat stress experienced inside the stroller to avoid the need for infants to sweat excessively to help prevent the insidious development of hypohydration which may further exacerbate the risk for morbidity [1].

Beside the risk of heat-related illness, infant heat stress may also result in thermal discomfort and disturbance to sleep patterns [39, 40]. Although the upper thermal limits for the avoidance of infant thermal discomfort are poorly understood, the maximum tolerable air temperature is thought to be in the region of 35°C for a naked baby and slightly lower when dressed [41] - only the *Muslin + Moist* and *Muslin + Moist + Fan* configurations succeeded in preventing the mean in-stroller temperature exceeding this threshold under the conditions assessed (see Table 2).

Translational importance

The current findings may inform evidence-based guidance regarding stroller heat safety management which may be disseminated to caregivers through healthcare services (e.g., antenatal classes, online health advice, etc). Evaporative cooling techniques may be advocated as efficacious stroller cooling strategies for use in hot weather. In contrast, caregivers should be advised to refrain from using dry material coverings that limit natural ventilation through the stroller as these exacerbate the heat stress within the carriage. The relevance of these findings may also translate to other settings in which infant thermal comfort is of concern. Evaporative cooling may also be suitable for use in indoor settings during hot weather when air conditioning is not readily available. For example, the use of a moist muslin cloth in conjunction with a fan may be feasibly employed to help cool the internal chamber of a bassinet/cot in which infants typically sleep. However, it acknowledged that future research is required to better understand the interaction between temperature, humidity, and outcomes such as infant comfort and sleep quality and to ultimately determine the efficacy of the tested cooling interventions in free living settings. Such cooling methods are simple and affordable and may therefore be employed as an accessible heat stress mitigation strategy when energy air-conditioning is inaccessible and/or prohibitively expensive, for example, in low- and middle- income countries [42].

Limitations

No human participants were involved in experimental testing and, therefore, it was not possible to assess the thermo-physiological consequences of the eight stroller configurations. However, the study design afforded well-controlled quantification of the thermal effects of each stroller configuration. Secondly, only one stroller type was tested, and it is therefore possible that the efficacy of the cooling techniques may vary if applied to a stroller of vastly different design and/or material composition. However, the current stroller was selected due to its generic

design and similarity to other commercially available infant strollers. Additionally, we acknowledge that we did not exhaust all possible cooling strategies (e.g., incorporation of ice blocks/phase change cooling materials into the stroller configuration), and therefore alternative cooling methods may also be efficacious. The cooling techniques were also only assessed over a 20-min period, so their efficacy remains unknown over an extended duration. Future research is required to examine the efficacy of cooling interventions during prolonged heat-stress exposures and to determine the extent to which these may help mitigate the level of heat stress experienced in the stroller carriage over time. However, when the moist muslin draping was employed, the amount of water remaining in the cloth after 20-min well exceeded the amount of water evaporated (Table 3). It is therefore expected that the *Muslin + Moist* and *Muslin + Moist + Fan* configurations would have continued to confer cooling benefit for at least an additional 20 min (40-min in total, assuming an evaporation rate of approximately 9 g/min). Moreover, the longevity of these simple cooling methods may be extended further by regular re-wetting the cloth using a hand-held water spray bottle. Further research is warranted to elucidate the critical time limits for these infant stroller evaporative cooling interventions - such information may be yielded using experimental methods like those used in the current study or via the use of thermal manikins which have been used previously to assess infant heat stress [23, 24]. However, our recommendation is that future research should prioritise examining the efficacy of stroller cooling interventions with human (infant) participants, enabling the physiological effects of in- stroller cooling to be examined.

As no infants were recruited to this study, the impact of metabolic heat production and insensible water losses (i.e., from the skin and respiratory system) was not assessed and, therefore, it is unknown to what extent this might have altered the in-stroller conditions had an infant been in situ. However, based on estimated resting infant metabolic rates and whole body sweat losses, in conjunction with the high air exchange within the stroller carriage, it is deemed

highly unlikely that the in-stroller temperature and/or humidity would have been elevated meaningfully. Additionally, the surface temperatures of the various stroller components were not assessed. As such, it is not possible to determine how the potential for conductive heat transfer between an infant and the stroller might have been impacted by the different stroller configurations. However, we consider the likely role of conductive heat transfer between stroller and infant to be negligible as the stroller carriage was completely shaded from direct solar radiation (either by the canopy or the canopy and cloth covering in combination), thus limiting the heating of the internal stroller surfaces. Furthermore, when positioned within the stroller carriage, the infant is in contact with the seat (i.e., the posterior aspect of the legs and torso), further shielding this material surface from solar radiation. From a human heat balance perspective, it is likely that dry heat exchange would occur primarily via convection, thus, we opted to focus on the measurement of the in-stroller air temperature. The use of thermistors suspended inside the stroller carriage was deemed both appropriate and practical for use in the current experimental set-up due to the shading provided by the stroller canopy (and material coverings), the consistent airflow through the carriage and the relatively stable environmental conditions. Additionally, the use of small thermistors enabled multiple temperature measurements, providing insight into the spatial variation inside the stroller. However, it should be acknowledged that this measurement technique may not be suitable in other settings in which such conditions are not met. For example, when the temperature sensors are exposed to direct solar radiation or when airflow is restricted, the use of a shaded and aspirated dry bulb thermometer in conjunction with a black globe temperature sensor is likely to be a more appropriate measurement tool.

Finally, whilst we opted to use the WBGT index to integrate the key environmental parameters and provide an assessment of the overall level of heat stress, we acknowledge that WBGT is not typically applied to compartment settings - this should be considered when

interpreting the differences observed inside the stroller carriage across the various configurations. However, it is important to note that WBGT was not used to inform decision making (i.e., to establish thresholds with which the efficacy of the cooling inventions was assessed) but, instead WBGT was simply used as a composite index to express the combined effects of multiple environmental parameters.

Conclusion

Our findings provide clear empirical evidence in support of the use of a moistened light-coloured muslin cloth draped over the entrance of the stroller carriage to reduce in-carriage infant stroller heat stress. The optimal cooling effect was achieved when a moist muslin draping was coupled with additional forced convection delivered by an inward facing battery-operated fan attached to the stroller frame. In contrast, other widely adopted stroller configurations exacerbated heat stress conditions inside the stroller. For example, the draping of a dry cloth (both muslin and flannelette) substantially worsened the heating of the stroller carriage and should, therefore, be advised against during periods of hot weather to help prevent dangerous levels of in-stroller heat stress.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

Experimental Study Three References

1. Brand, M.C. and H.A. Shippey, *Thermoregulation*, in *Core Curriculum for Neonatal Intensive Care Nursing*, M.T. Verklan, Editor. 2021, Elsevier: St. Louis, Missouri. p. 86-98.
2. Gardner, S.L. and B.H. Cammack, *Heat Balance*, in *Merenstein & Gardner's Handbook of Neonatal Intensive Care, Ninth Edition*, S.L. Gardner, Editor. 2021, Elsevier Inc.: St. Louis, Missouri. p. 137-164.
3. Fleming, P.J., et al., *Interaction between bedding and sleeping position in the sudden infant death syndrome: a population based case-control study*. British Medical Journal, 1990. **301**(6743): p. 85-89.
4. Guntheroth, W.G. and P.S. Spiers, *Thermal Stress in Sudden Infant Death: Is There an Ambiguity With the Rebreathing Hypothesis?* Pediatrics 2001. **107**(4): p. 693-698.
5. Elhaik, E., *Neonatal circumcision and prematurity are associated with sudden infant death syndrome (SIDS)*. Journal of Clinical and Translational Research, 2019. **4**(2): p. 136-151.
6. Inoue, Y., T. Kuwahara, and T. Araki, *Maturation-and aging-related changes in heat loss effector function*. Journal of Physiological Anthropology and Applied Human Science, 2004. **23**(6): p. 289-294.
7. Székely, M. and J. Garai, *Thermoregulation and age*. Handbook of Clinical Neurology, 2018. **156**: p. 377-395.
8. CDC. *Centers for Disease Control and Prevention: Births and Natality*. 2023; Available from: <https://www.cdc.gov/nchs/fastats/births.htm>.
9. Bull, F.C., et al., *World Health Organization 2020 guidelines on physical activity and sedentary behaviour*. British Journal of Sports Medicine, 2020. **54**(24): p. 1451-1462.

10. Currie, J.L. and E. Develin, *Stroll Your Way To Well-Being: A Survey Of The Perceived Benefits, Barriers, Community Support, And Stigma Associated With Pram Walking Groups Designed For New Mothers, Sydney, Australia*. Health Care for Women International, 2002. **23**(8): p. 882-893.
11. Birken, C.S., et al., *Parents' perception of stroller use in young children: a qualitative study*. BMC Public Health, 2015. **15**(808).
12. Sehat, A.R., U. Nirmal, and Z. Jin, *State of the art baby strollers: Design review and the innovations of an ergonomic baby stroller*. Cogent Engineering, 2017. **4**(1).
13. NSW Health. *Babies and children in the heat*. 2022; Available from: <https://www.health.nsw.gov.au/environment/beattheheat/Pages/babies-children-hot-weather.aspx>.
14. National Health Service (NHS). *Keeping your baby safe in the sun*. 2021; Available from: <https://www.nhs.uk/conditions/baby/first-aid-and-safety/safety/safety-in-the-sun/>.
15. Green, A.C., S.C. Wallingford, and P. McBride, *Childhood exposure to ultraviolet radiation and harmful skin effects: Epidemiological evidence*. Progress in Biophysics and Molecular Biology, 2011. **107**(3): p. 349-355.
16. Burnie, R. and C. Howe. *Pram covers can overheat children inside, safety experts warn* 2019; Available from: <https://www.abc.net.au/news/2019-01-17/pram-covers-can-overheat-children-safety-experts-warn/10721062>.
17. Holmberg, H. *Swedes risk infants' lives by covering up prams*. . The Local 2014; Available from: <https://www.thelocal.se/20140711/swedes-risk-infants-lives-by-covering-up-prams>.
18. Graham, C., et al., *Optimal break structures and cooling strategies to mitigate heat stress during a Rugby League match simulation*. Journal of Science and Medicine in Sport, 2021. **24**(8): p. 793-799.

19. Lynch, G.P., et al., *Optimal cooling strategies for players in Australian Tennis Open conditions*. Journal of Science and Medicine in Sport, 2018. **21**(3): p. 232-237.
20. Mitchell, J.B., B.K. McFarlin, and J.P. Dugas, *The Effect of Pre-Exercise Cooling on High Intensity Running Performance in the Heat*. International Journal of Sports Medicine, 2003. **24**(2): p. 118-124.
21. Morris, N.B., et al., *A Preliminary Study of the Effect of Dousing and Foot Immersion on Cardiovascular and Thermal Responses to Extreme Heat*. JAMA : the journal of the American Medical Association, 2019. **322**(14): p. 1411-1413.
22. Cramer, M.N., et al., *Keeping older individuals cool in hot and moderately humid conditions: wetted clothing with and without an electric fan*. Journal of Applied Physiology 2020. **128**(3): p. 604-611.
23. Danielsson, U., *Heat and mass transfer from a baby manikin: impact of a chemical warfare protective bag*. European Journal of Applied Physiology, 2004. **92**(6): p. 689-693.
24. Lahana, A., et al., *Warming the premature infant in the delivery room: Quantification of the risk of hyperthermia*. Medical Engineering & Physics, 2018. **59**: p. 70-74.
25. Ravanelli, N.M., Hodder, S. G., Havenith, G., & Jay, O., *Heart rate and body temperature responses to extreme heat and humidity with and without electric fans*. JAMA: The Journal of the American Medical Association, 2015. **313**(7): p. 724-725.
26. Hospers, L., et al., *Electric fans: A potential stay-at-home cooling strategy during the COVID-19 pandemic this summer?* Science of the Total Environment, 2020. **747**: p. 141180.
27. Foster, J., et al., *Quantifying the impact of heat on human physical work capacity; part II: the observed interaction of air velocity with temperature, humidity, sweat rate, and*

- clothing is not captured by most heat stress indices*. International Journal of Biometeorology, 2022. **66**(3): p. 507-520.
28. Morris, N.B., et al., *Electric fan use for cooling during hot weather: a biophysical modelling study*. The Lancet: Planetary Health, 2021. **5**(6): p. e368-e377.
 29. Harpin, V., G. Chellappah, and N. Rutter, *Responses of the newborn infant to overheating*. Biology of the Neonate, 1983. **44**(2): p. 65-75.
 30. Foster, K.G., E.N. Hey, and G. Katz, *The response of the sweat glands of the new born baby to thermal stimuli and to intradermal acetylcholine*. Journal of Physiology, 1969. **203**: p. 13-29.
 31. McLaren, C., J. Null, and J. Quinn, *Heat stress from enclosed vehicles: moderate ambient temperatures cause significant temperature rise in enclosed vehicles*. Pediatrics, 2005. **116**(1): p. e109-12.
 32. Vanos, J.K., et al., *Evaluating the impact of solar radiation on pediatric heat balance within enclosed, hot vehicles*. Temperature, 2018. **5**(3): p. 276-292.
 33. O'Callaghan, P.W. and S.D. Probert, *Thermal insulation provided by dry, single-layer clothing materials*. Applied Energy, 1976. **2**(4): p. 269-277.
 34. Alay, S., C. Alkan, and F. Göde, *Steady-state thermal comfort properties of fabrics incorporated with microencapsulated phase change materials*. The Journal of The Textile Institute, 2012. **103**(7): p. 757-765.
 35. Scipioni, M., E. Silva, and F. Farahi, *Solar Absorption Index (SAI) as a Parameter to Assess the Coolness of Fabrics Exposed to Sunlight*. Fibres and Textiles in Eastern Europe, 2020. **28**(5(143)): p. 44-49.
 36. Rutter, N. and D. Hull, *Response of term babies to a warm environment*. Archives of Disease in Childhood, 1979. **54**(3): p. 178-183.

37. Sulyok, E., E. Jéquier, and L.S. Prod'hom, *Respiratory contribution to the thermal balance of the newborn infant under various ambient conditions*. Pediatrics (Evanston), 1973. **51**(4): p. 641-650.
38. Garcia-Souto, M.D.P. and P. Dabnichki, *Core and local skin temperature: 3–24 months old toddlers and comparison to adults*. Building and Environment, 2016. **104**: p. 286-295.
39. Wailoo, M.P., S.A. Petersen, and H. Whitaker, *Disturbed nights and 3-4 month old infants: the effects of feeding and thermal environment*. Archives of Disease in Childhood, 1990. **65**(5): p. 499-501.
40. Filingeri, D., et al., *The effects of clothing layers on the thermoregulatory responses to short duration babywearing in babies under 12 months old*. Physiological Reports, 2020. **8**(9): p. e14425-n/a.
41. WHO, *Thermal Protection of the Newborn: a practical guide*. 1997, World Health Organisation: Geneva.
42. Global, L., GOGLA, and ESMAP, *Off-Grid Solar Market Trends Report 2020*, W.B. Group, Editor. 2020, International Finance Corporation. p. 304.

CHAPTER 8: GENERAL DISCUSSION AND THESIS CONCLUSIONS

Summary

This thesis sought to investigate strategies to mitigate thermal strain in infancy in targeted clinical and free-living environmental scenarios, with the specific aims of:

- A) comparing the suitability and level of agreement in using a skin site on the neck over the carotid artery (T_{neck}) – which has previously been shown to be a promising method in anaesthetised children undergoing elective general surgery – with the traditional method used currently (T_{feedback}) as a surrogate measure of an invasive core (rectal) temperature (T_{rec}) in infants nursed under a radiant warmer (Chapter 3).
- B) comparing the suitability and level of agreement of potential skin contact temperature sites – specifically the lower back region (T_{back}) when an infant is lying in supine, and on the chest (T_{chest}) when an infant is lying in prone – with the traditional method used currently (T_{feedback}) as a surrogate measure of core temperature measured rectally (T_{rec}) in infants nursed under a radiant warmer (Chapter 5).
- C) empirically examining the cooling efficacy of eight different low-cost stroller configurations, to reduce the heat stress experienced inside an infant stroller carriage in hot and moderately humid weather conditions (Chapter 7).

This thesis has demonstrated that the current method of estimating core temperature using a skin temperature measurement with a sensor along the mid-axillary line has extremely poor accuracy in premature infants nursed under radiant warmers in the neonatal intensive care unit. As such, this may lead to bouts of overheating and/or underheating of the infant, thus increasing the risk of physiological stress as the infant experiences thermal strain in this clinical environment. Another setting in which infants can potentially experience thermal strain is when being pushed in a stroller during periods of hot weather. This thesis addresses this common issue by investigating optimal cooling interventions that are low-cost and reproducible in everyday settings.

In Chapters 3 and 5, alternative skin sites for temperature sensor placement were assessed for their level of agreement with rectal temperature and overall feasibility. Chapter 3 established the better utility of using T_{neck} as a non-invasive estimate of core temperature compared with the traditional T_{feedback} site over the mid-axillary line along the side of the thorax. However, there remained a tendency for T_{neck} to yield highly variable estimates of core temperature and systematically underestimated temperature compared with that measured in the rectum. In Chapter 5, it was demonstrated that placing temperature sensors at strategic contact skin sites i.e., on the lower back in the supine position, and on the chest in the prone position, resulted in very high levels of agreement with rectal temperature due to the principle of zero heat flux. These findings indicate that measuring skin temperature at a site that is in continual contact with the mattress provides the optimal non-invasive estimate of core temperature.

In Chapter 7, the issue of infant heat stress in the context of baby strollers was assessed. It was shown with clear evidence that during 20-minute bouts in hot, sunny, and moderately humid weather, stroller covering configurations that incorporated a source of evaporative cooling (i.e., moistened muslin coverings coupled with fan use), effectively reduced the ambient temperature within the stroller carriage by 4.7°C, when compared to a standard-practice stroller configuration. In contrast, the common practice of shading the stroller with a dry muslin or flannelette covering, substantially increased the in-stroller temperature by 2.6°C and 3.7°C respectively, potentially increasing the risk for heat-related discomfort and/or heat-related illness.

Detailed findings of these studies are discussed in the respective chapters within this thesis. The subsequent section discusses the broader implications of these findings and highlights opportunities for further research in these areas.

Implications and future directions

Non-invasive methods for monitoring core temperature in infants nursed under radiant warmers

Previous studies have investigated using alternative skin sites, aside from T_{feedback} , as non-invasive methods to estimate body temperature in this population of infants [1-3]. However, these previous studies had certain limitations when translating the findings into overarching clinical practice, such as short data collection durations, or observing infants who were sedated throughout the data collection process [1, 4]. Therefore, this thesis aimed to address these potential limitations by exploring a longer observation period of 4 hours in tandem with current nursing practice of temperature monitoring [5], and with infants who were generally well and alert when awake, providing evidence to inform more practical applications in clinical NICU practice.

Chapter 3 and 5 demonstrated that T_{feedback} exhibited an inferior level of agreement when compared to T_{neck} and the contact skin sites (T_{back} and T_{chest}). Importantly, T_{back} and T_{chest} - when in contact with the mattress - provided an even better estimation of core temperature compared with T_{neck} . We therefore present strong evidence to propose that current NICU guidelines should be updated to recommend the use of skin-contact sites to derive a more accurate non-invasive estimation of core temperature, as these alternative skin sites have demonstrated their feasibility and suitability for use in clinical settings to aid in the thermal monitoring of premature infants. This argument represents a clear shift away from the recommendations commonly promoted in clinical settings, for example, that “axillary and abdominal skin temperatures are the preferred sites for measuring skin temperature” [5] or that after initial determination of baseline rectal temperature, axillary temperature should be taken thereafter as regular surrogate measure of core temperature [6].

Furthermore, the application of the temperature sensors on these alternative skin sites will have minimal to no disruption to current clinical practice due to ease of access to these sites.

Future research can investigate the suitability of these skin sites on infants of a wider postnatal age range and determine if similar results can be demonstrated on different radiant warmer brands and models. A potential advancement to the application of the zero heat flux phenomenon is to consider reducing the reliance of temperature sensors attached to the relatively fragile infant skin. These sensors could be incorporated into the design of the radiant warmer mattress itself, which will allow continual measurement of skin contact temperature, regardless of infant position. This method may potentially eradicate potential issues such as dislodgement of temperature sensors and irritation to the infant skin due to prolonged use [7]. This innovation can be applied in other settings too where invasive core temperature measurements are impractical, such as in baby cot mattresses during sleeping, or in car seats.

Cooling strategies for infant strollers during hot weather

Whilst there had been some previous discussion concerning the detrimental effects of stroller usage and cloth coverings in hot weather [8-10], these have typically focused on rather speculative concerns around air quality (e.g., a build-up of carbon dioxide within the stroller) and the potential deprivation of Vitamin D as a result of reduced sun exposure [8]. All previous discussion around the potential issue of in-stroller heat stress appears to originate from newspaper interviews and is built upon extremely weak scientific foundations. The only “evidence” that has been identified stems from a newspaper interview after which the journalists conducted a very crude 90-min experiment which revealed a heating effect of covering a completely static pram during hot weather [11]. However, the method used to quantify the in-stroller temperature was not described, nor were any additional experimental controls detailed. The static nature of the stroller in this “study” is also extremely unrealistic as it is unlikely that parents and caregivers will leave their infants in such a vulnerable position. Infant behavioural symptoms i.e., crying, when experiencing heat stress, would also alert the parent to tend to the infant, further reducing

the likelihood of a caregiver leaving their child in a static stroller exposed to extended periods of solar radiation. Furthermore, no study had previously investigated low-cost cooling strategies for outdoor stroller use in hot weather, hence Chapter 7 explored a novel approach to address this research aim and offer practical solutions. Our attempt to create awareness in public and professional domains, was aided by the considerable media interest the publication of the manuscript attracted, including national feature pieces on ABC and Channel 9 news, a widely read Conversation article and over 410,000 views on Instagram (see Appendix E).

Chapter 7 was designed as a proof-of-concept study to test various potential methods to effectively cool a stroller carriage during periods of hot weather. Due to the untested nature of the stroller interventions, there was a possibility that the interventions could increase the temperature within the stroller carriage considerably, thus potentially harming an infant in the testing process. This consideration was the primary reason for not conducting this study with human infant participants. Indeed, the heating of the stroller carriage was substantially accelerated when covered with a dry material draping (i.e., using a muslin or flannelette cloth). In contrast, the use a moistened muslin covering, with and without the use of a clip-on fan, effectively cooled the stroller carriage, when compared to the conventional stroller set up with the stroller canopy in a propped down position. The data provide clear empirical evidence in support of the efficacy of the abovementioned interventions. Future research is now warranted to investigate their efficacy of these strategies to mitigate the physiological strain experienced by human infant participants exposed to hot weather when transported in strollers. Outcome variables that may be considered from the infant's perspective include infant behaviour (e.g., irritability, restlessness, etc.) and sleep quality. Additionally, the thermal comfort of the infant, as perceived by the parent, may be of particular interest. Furthermore, the measurement of body core temperature – either via rectal thermometry or non-invasive axillary temperature – and skin temperature would help establish the efficacy of stroller cooling strategies to mitigate the

physiological thermal strain experienced by infants whilst housed in a stroller. Other parameters such as heart rate and oxygen saturation may also be measured to monitor the infant's physiological status in response to stroller cooling.

When designing the Chapter 7 experimental protocol, it was reasoned that a 20-minute bout would be a sufficient length of time to simulate a stroller in transit from one destination to another. The findings highlighted that the effects of the evaporative cooling tended to plateau before the end of the 20-minute bout. Based on our findings, we can safely estimate that the muslin covering would dry out by around the 40-minute mark, eliminating the evaporative cooling effect. Further research can investigate the sustained effect of evaporative cooling, by intermittently moistening the muslin coverings using a simple spray bottle, for example, every 5 minutes, instead of only at the start of the intervention as conducted in our study.

The experimental protocol also utilised a predetermined route and fixed walking speed within the boundaries of an outdoor area outside a laboratory building. This serves well in terms of ensuring standardisation during the testing phase. With our study findings in mind, future research can consider the manipulation of other environmental components, such as conducting the study in an outdoor park versus a built-up high rise urban environment, with different walking and running speeds, to determine if our findings can be translated to these settings. Likewise, the trials in this study were all conducted in hot and moderately humid weather. The efficacy of stroller cooling interventions should be examined in different climate conditions (e.g., hot and dry, with and without wind), as these conditions could impact the rate of evaporation from the muslin coverings and influence the effectiveness of the evaporative cooling interventions. Additionally, the effectiveness of the stroller cooling strategies in hot and very humid conditions as experienced in tropical and equatorial environments e.g., in countries such as India, Pakistan, Singapore and Brazil, requires further investigation.

Other variables can also be considered to further test the robustness of Chapter 7's findings. The thesis study only tested a single type (brand) of muslin covering that was commercially available in Australia. Different muslin brands with varying weave densities – as well as different absorbent materials – should be tested in the future, as the material characteristics (i.e., weave, thickness etc.) may affect the rate of water evaporation, influencing the evaporative cooling effect. The muslin covering was also draped in a single layer only as a means of standardising the testing protocol. It is uncertain if added muslin layers would elicit similar findings, as adding layers may allow for a greater total volume of water to be absorbed by the draping. This might in turn extend the time taken to dry itself out, which will then extend the duration of effective evaporative cooling. The clip-on battery-operated fan with foam blades used in the study elicited a maximal fan speed of ~ 1 m/s. Other fan types eliciting higher, or lower, fan speeds can be tested to determine if any addition or reduction in forced convection will alter the magnitude of cooling when used in combination with a wet draping. Furthermore, our study only utilised tap water at room temperature for moistening. This was decided to facilitate the ease of attaining the water source. However, future research can also look into the temperature of the water e.g., refrigerated water, as a variable to compare the resting baseline temperature and subsequent rates of evaporative cooling.

An additional limitation of Chapter 7 is that only one stroller type was used throughout the study. This was considered to be an appropriate method to standardise the experimental protocol. However, as there are a multitude of variations in stroller and pram configurations that are commercially available, further research is required to determine if our findings also apply to alternative strollers with differing materials and carriage configurations. Finally, in a similar vein to Chapter 5's findings, a potential advancement to the temperature monitoring of the stroller carriage configuration may be the development of a temperature sensor embedded within the stroller, or the use of materials that better help cool the in-stroller environmental conditions.

These innovations may be useful to help better monitor the stroller conditions during periods of hot weather and help facilitate a proactive approach to stroller heat management.

Thesis conclusions

This thesis explored various targeted strategies to measure and mitigate thermal stress in two different scenarios to help optimise infant care. In the clinical setting, Chapters 3 and 5 have demonstrated that in infants nursed under radiant warmers, alternative skin sites provide a superior surrogate measurement of core temperature, as demonstrated by their higher level of agreement with infant rectal temperature, when compared to the traditionally used T_{feedback} site. In Chapter 3, skin temperature over the carotid artery was shown to provide a better estimate of rectal temperature compared with T_{feedback} , however, high measurement variability and a systematic underestimation of core temperature remained common. Chapter 5 demonstrated that even closer agreement with rectal temperature could be obtained from skin contact sites at which zero heat flux between the infant body and the surrounding environment could be achieved. Deriving an estimate of core temperature from zero heat flux skin contact sites may represent the optimal non-invasive measurement method for use in NICU settings.

In Chapter 7, the free-living efficacy of various low-cost and sustainable stroller cooling interventions was examined. The findings clearly demonstrate the utility of a wet muslin covering combined with a battery-operated fan to mitigate the severity of heat stress experienced inside a stroller carriage during hot and moderately humid weather. Chapter 7 also highlighted methods that should be avoided in these weather conditions, such as the use of a dry muslin covering and flannelette. It is hoped that these findings will result in updated heat-health advice and guidance for dissemination to parents/caregivers during periods of extreme heat to help protect infants when being transported in a stroller. Overall, the findings contained within this thesis should be considered in the context of infant heat-health decision making in both clinical and free-living public health settings.

General Discussion and Thesis Conclusions References

1. Blackburn, S., et al., *Neonatal thermal care, part III: The effect of infant position and temperature probe placement*. Neonatal Network, 2001. **20**(3): p. 25-30.
2. Fraguera, A., F.D. Matlalcutzi, and A.M. Ramos, *Mathematical modelling of thermoregulation processes for premature infants in closed convectively heated incubators*. Computers in Biology and Medicine, 2015. **57**: p. 159-72.
3. Jirapaet, V. and K. Jirapaet, *Comparisons of tympanic membrane, abdominal skin, axillary, and rectal temperature measurements in term and preterm neonates*. Nursing & Health Sciences, 2000. **2**(1): p. 1-8.
4. Bissonnette, B., D.I. Sessler, and P. Laflamme, *Intraoperative temperature monitoring sites in infants and children and the effect of inspired gas warming on esophageal temperature*. Anesthesia and Analgesia, 1989. **69**(2): p. 192-196.
5. The Children's Hospital at Westmead, *Thermoregulation in Neonatal Care*. 2021, Sydney Children's Hospital Network, Australia.
6. The Royal Children's Hospital Melbourne. *Assisted Thermoregulation*. Clinical Guidelines (Nursing) 2020; Available from: https://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Thermoregulation_in_the_Preterm_Infant/#management.
7. Lund, C., *Medical Adhesives in the NICU*. Newborn and Infant Nursing Reviews, 2014. **14**(4): p. 160-165.
8. Burnie, R. and C. Howe. *Pram covers can overheat children inside, safety experts warn* 2019; Available from: <https://www.abc.net.au/news/2019-01-17/pram-covers-can-overheat-children-safety-experts-warn/10721062>.
9. Christian, N. *Heatwave warning: Common pram habit could be potentially fatal for babies and young kids*. 2019; Available from:

<https://thewest.com.au/lifestyle/parenting/heatwave-warning-common-pram-habit-could-be-potentially-fatal-for-babies-and-young-kids-ng-81b054ca62b17dd6cd7c6b651c14a6a9>.

10. Wilson, L., S. Quine, and M. Lewis, *Hiding under the blankets: reasons why parents cover infants' strollers and prams*. Neonatal, Paediatric, and Child Health Nursing, 2010. **13**(2): p. 13-17.
11. Holmberg, H. *Swedes risk infants' lives by covering up prams*. . The Local 2014; Available from: <https://www.thelocal.se/20140711/swedes-risk-infants-lives-by-covering-up-prams>.

THESIS BIBLIOGRAPHY

- ABS. (2022). Australian Bureau of Statistics: National, state and territory population. Retrieved from <https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/latest-release>
- Adamson, J. S. K., & Towell, M. E. (1965). Thermal homeostasis in the fetus and newborn. *Anesthesiology*, 26(4), 531-548. doi:10.1097/00000542-196507000-00017
- Aherne, W., & Hull, D. (1966). Brown adipose tissue and heat production in the newborn infant. *Journal of Pathology and Bacteriology*, 91, 223-234.
- Alay, S., Alkan, C., & Göde, F. (2012). Steady-state thermal comfort properties of fabrics incorporated with microencapsulated phase change materials. *The Journal of The Textile Institute*, 103(7), 757-765. doi:10.1080/00405000.2011.606982
- Australia, S. M. (2016). SMA Position Statement Exercise in Pregnancy and the Postpartum Period. Retrieved from www.sma.org.au: <https://sma.org.au/wp-content/uploads/2016/09/SMA-Position-Statement-Exercise-Pregnancy.pdf>
- Basaga, xf, a, X., Sartini, C., Barrera, G., xf, . . . n, M. (2011). Heat Waves and Cause-specific Mortality at all Ages. *Epidemiology*, 22(6), 765-772.
- Baumgart, S. (1990). Radiant heat loss versus radiant heat gain in premature neonates under radiant warmers. *Biology of the Neonate*, 57(1), 10.
- Baumgart, S. (2008). Iatrogenic hyperthermia and hypothermia in the neonate. *Clinics in Perinatology*, 35(1), 183-197, ix-x. doi:10.1016/j.clp.2007.11.002
- BBC. (2022). BBC News. Climate change: Europe's warm summer shatters records. Retrieved from <https://www.bbc.com/news/science-environment-62833937>
- Bell, E. F. (1983). Infant incubators and radiant warmers. *Early Human Development*, 8(3), 351-375. doi:10.1016/0378-3782(83)90018-X
- Bernardo, L. M., Henker, R., & O'Connor, J. (1999). Temperature measurement in pediatric trauma patients: A comparison of thermometry and measurement routes. *Journal of Emergency Nursing*, 25(4), 327-329. doi:S009917679900135X [pii]
- Bettley, F., & Grice, K. A. (1965). A method for measuring the transepidermal water loss and a means of inactivating sweat glands. *British journal of Dermatology*, 77(12), 627-638. doi:10.1111/j.1365-2133.1965.tb14594.x

- Birken, C. S., Lichtblau, B., Lenton-Brym, T., Tucker, P., Maguire, J. L., Parkin, P. C., & Mahant, S. (2015). Parents' perception of stroller use in young children: a qualitative study. *BMC Public Health*, 15(808).
- Bissonnette, B. (1992). Temperature monitoring in pediatric anesthesia. *International Anesthesiology Clinincs*, 30(3), 63-76.
- Bissonnette, B. (2011). Pediatric Anesthesia: Basic Principles. In B. Bissonnette (Ed.), *Temperature Regulation: physiology and pharmacology* (pp. 221-258). Shelton, CT: People's Medical Publishing House-USA.
- Bissonnette, B., Sessler, D. I., & Laflamme, P. (1989). Intraoperative temperature monitoring sites in infants and children and the effect of inspired gas warming on esophageal temperature. *Anesthesia and Analgesia*, 69(2), 192-196. doi:10.1213/00000539-198908000-00009
- Blackburn, S., DePaul, D., Loan, L. A., Marbut, K., Taquino, L. T., Thomas, K. A., & Wilson, S. K. (2001). Neonatal thermal care, part III: The effect of infant position and temperature probe placement. *Neonatal Network*, 20(3), 25-30. doi:10.1891/0730-0832.20.3.25
- Brand, M. C., & Shippey, H. A. (2021). Thermoregulation. In M. T. Verklan (Ed.), *Core Curriculum for Neonatal Intensive Care Nursing* (6th ed., pp. 86-98). St. Louis, Missouri: Elsevier.
- Brown, W. J., Hayman, M., Haakstad, L. A. H., Lamerton, T., Mena, G. P., Green, A., . . . Mielke, G. I. (2022). Australian guidelines for physical activity in pregnancy and postpartum. *Journal of Science and Medicine in Sport*, 25(6), 511-519. doi:https://doi.org/10.1016/j.jsams.2022.03.008
- Bull, F. C., Al-Ansari, S. S., Biddle, S., Borodulin, K., Buman, M. P., Cardon, G., . . . Chou, R. (2020). World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *British Journal of Sports Medicine*, 54(24), 1451-1462. doi:10.1136/bjsports-2020-102955
- Burnie, R., & Howe, C. (2019). Pram covers can overheat children inside, safety experts warn Retrieved from <https://www.abc.net.au/news/2019-01-17/pram-covers-can-overheat-children-safety-experts-warn/10721062>
- CDC. (2023). Centers for Disease Control and Prevention: Births and Natality. Retrieved from <https://www.cdc.gov/nchs/fastats/births.htm>

- Chang, A. B., Wilson, S. J., Masters, I. B., Yuill, M., Williams, J., Williams, G., & Hubbard, M. (2003). Altered arousal response in infants exposed to cigarette smoke. *Archives of Disease in Childhood*, 88(1), 30-33. doi:10.1136/adc.88.1.30
- Chaseling, G. K., Molgat-Seon, Y., Daboval, T., Chou, S., & Jay, O. (2016). Body temperature mapping in critically ill newborn infants nursed under radiant warmers during intensive care. *Journal of Perinatology*, 36(7), 540-543. doi:10.1038/jp.2016.16
- Chitty, H., & Wyllie, J. (2013). Importance of maintaining the newly born temperature in the normal range from delivery to admission. *Seminars in Fetal Neonatal Medicine*, 18(6), 362-368. doi:10.1016/j.siny.2013.08.002
- Christensen, R. D., Pysher, T. J., & Christensen, S. S. (2007). Case report: perianal necrotizing fasciitis in a near-term neonate. *Journal of Perinatology*, 27(6), 390-391. doi:10.1038/sj.jp.7211733
- Christian, N. (2019). Heatwave warning: Common pram habit could be potentially fatal for babies and young kids. Retrieved from <https://thewest.com.au/lifestyle/parenting/heatwave-warning-common-pram-habit-could-be-potentially-fatal-for-babies-and-young-kids-ng-81b054ca62b17dd6cd7c6b651c14a6a9>
- Çınar, N. D., & Filiz, T. M. (2006). Neonatal thermoregulation. *Journal of Neonatal Nursing*, 12(2), 69-74. doi:10.1016/j.jnn.2006.01.006
- Cramer, M. N., Huang, M., Moralez, G., & Crandall, C. G. (2020). Keeping older individuals cool in hot and moderately humid conditions: wetted clothing with and without an electric fan. *Journal of Applied Physiology*, 128(3), 604-611. doi:10.1152/japplphysiol.00786.2019
- Cramer, M. N., & Jay, O. (2016). Biophysical aspects of human thermoregulation during heat stress. *Autonomic Neuroscience*, 196, 3-13. doi:10.1016/j.autneu.2016.03.001
- Currie, J. L., & Develin, E. (2002). Stroll Your Way to Well-Being: A Survey Of The Perceived Benefits, Barriers, Community Support, And Stigma Associated With Pram Walking Groups Designed For New Mothers, Sydney, Australia. *Health Care for Women International*, 23(8), 882-893. doi:10.1080/07399330290112380
- Dahyot-Fizelier, C., Lamarche, S., Kerforne, T., Benard, T., Giraud, B., Bellier, R., . . . Mimoz, O. (2017). Accuracy of Zero-Heat-Flux Cutaneous Temperature in

- Intensive Care Adults. *Critical Care Medicine*, 45, e715–e717. DOI: 10.1097/CCM.0000000000002317
- The dangers of covering your pram. (2022). Retrieved from <https://rednose.org.au/news/the-dangers-of-covering-your-pram>
- Danielsson, U. (2004). Heat and mass transfer from a baby manikin: impact of a chemical warfare protective bag. *European Journal of Applied Physiology*, 92(6), 689-693. doi:10.1007/s00421-004-1133-2
- Del Bene, V. (1990). Temperature. In H. W. D. Walker H.K., Hurst J.W. (Ed.), *Clinical Methods: The History, Physical, and Laboratory Examinations*. (3rd ed.). Boston: Butterworths.
- Dobbinson, S. P., Wakefield, M. P., Hill, D. P., Girgis, A. P., Aitken, J. F. P., Beckmann, K. M. P. H., . . . Bowles, K.-A. B. (2012). Children's sun exposure and sun protection: Prevalence in Australia and related parental factors. *Journal of the American Academy of Dermatology*, 66(6), 938-947. doi:10.1016/j.jaad.2011.06.015
- Dollberg, S., Atherton, H. D., Sigda, M., Acree, C. M., & Hoath, S. B. (1994). Effect of insulated skin probes to increase skin-to-environmental temperature gradients of preterm infants cared for in convective incubators. *The Journal of Pediatrics*, 124(5), 799-801. doi:10.1016/S0022-3476(05)81377-0
- Du Bois, D. and Du Bois E.F (1916). A formula to estimate the approximate surface area if height and weight be known. *Archives of Internal Medicine*, 17:863-71
- Ebi, K. L., Capon, A., Berry, P., Broderick, C., de Dear, R., Havenith, G., . . . Ollie, J. (2021). Hot weather and heat extremes: health risks. *The Lancet*, 398(10301), 698-708. doi:[https://doi.org/10.1016/S0140-6736\(21\)01208-3](https://doi.org/10.1016/S0140-6736(21)01208-3)
- El-Radhi, A. S., & Barry, W. (2006). Thermometry in paediatric practice. *Archives of Disease in Childhood*, 91(4), 351-356. doi:91/4/351 [pii]10.1136/adc.2005.088831
- El-Radhi, A. S., & Patel, S. (2006). An evaluation of tympanic thermometry in a paediatric emergency department. *Emergency Medicine Journal*, 23(1), 40-41. doi:23/1/40 [pii] 10.1136/emj.2004.022764
- Elhaik, E. (2019). Neonatal circumcision and prematurity are associated with sudden infant death syndrome (SIDS). *Journal of Clinical and Translational Research*, 4(2), 136-151.

- Elliott, R. I., & Mann, T. P. (1957). Neonatal cold injury due to accidental exposure to cold. *Lancet* (London, England), 272(6962), 229.
- Ellis, J. (2005). Neonatal hypothermia. *Journal of Neonatal Nursing*, 11(2), 76-82. doi:<https://doi.org/10.1016/j.jnn.2005.04.010>
- Erickson, R. S., & Woo, T. M. (1994). Accuracy of infrared ear thermometry and traditional temperature methods in young children. *Heart Lung*, 23(3), 181-195.
- Eshraghi, Y., Nasr, V., Parra-Sanchez, I., Van Duren, A., Botham, M., Santoscoy, T., & Sessier, D. (2014). An Evaluation of a Zero-Heat-Flux Cutaneous Thermometer in Cardiac Surgical Patients. *Anesthesia and Analgesia*, 119, 543-549. doi:10.1213/ANE.0000000000000319
- Eurostat. (2023). Fertility statistics. Retrieved from https://ec.europa.eu/eurostat/statisticsexplained/index.php?title=Fertility_statistics
- Fic, A. M., Ingham, D. B., Ginalski, M. K., Nowak, A. J., & Wrobel, L. (2010). Heat and mass transfer under an infant radiant warmer--development of a numerical model. *Medical Engineering and Physics*, 32(5), 497-504. doi:10.1016/j.medengphy.2010.02.021
- Filingeri, D., Cowley, H., Merrick, C., Gang, P. S., & Filingeri, V. L. (2020). The effects of clothing layers on the thermoregulatory responses to short duration babywearing in babies under 12 months old. *Physiological Reports*, 8(9), e14425-n/a. doi:10.14814/phy2.14425
- Fleming, P. J., Gilbert, R., Azaz, Y., Berry, P. J., Rudd, P. T., Stewart, A., & Hall, E. (1990). Interaction between bedding and sleeping position in the sudden infant death syndrome: a population based case-control study. *British Medical Journal*, 301(6743), 85-89. doi:10.1136/bmj.301.6743.85
- Flenady, V., & Woodgate, P. G. (2009). Radiant warmers versus incubators for regulating body temperature in newborn infants (review). *Cochrane Database of Systematic Reviews* (2), 1-41.
- Foster, J., Smallcombe, J. W., Hodder, S., Jay, O., Flouris, A. D., & Havenith, G. (2022). Quantifying the impact of heat on human physical work capacity; part II: the observed interaction of air velocity with temperature, humidity, sweat rate, and clothing is not captured by most heat stress indices. *International Journal of Biometeorology*, 66(3), 507-520. doi:10.1007/s00484-021-02212-y

- Foster, K. G., Hey, E. N., & Katz, G. (1969). The response of the sweat glands of the newborn baby to thermal stimuli and to intradermal acetylcholine. *Journal of Physiology*, 203, 13-29. doi:<https://doi.org/10.1113/jphysiol.1969.sp008846>
- Fox, R. H., Solman, A. J., Isaacs, R., Fry, A. J., & Macdonald, I. C. (1973). A New Method for Monitoring Deep Body Temperature from the Skin Surface. *Clinical Science and Molecular Medicine*, 44(1), 81-86. doi:/10.1042/cs0440081
- Fraguela, A., Matlalcuatzi, F. D., & Ramos, A. M. (2015). Mathematical modelling of thermoregulation processes for premature infants in closed convectively heated incubators. *Computers in Biology and Medicine*, 57, 159-172. doi:10.1016/j.compbimed.2014.11.021
- Frank, J. D., & Brown, S. (1978). Thermometers and rectal perforations in the neonate. *Archives of Disease in Childhood*, 53(10), 824-825. doi:10.1136/ad.53.10.824
- Gagge, A. P., & Nishi, Y. (2010). Heat Exchange Between Human Skin Surface and Thermal Environment. In (pp. 69-92). Hoboken, NJ, USA: John Wiley & Sons, Inc.
- Gandy, G. M., Adamsons, J. K., Cunningham, N., Silverman, W. A., & James, L. S. (1964). Thermal environment and acid-based homeostasis in human infants during the first few hours of life. *The Journal of Clinical Investigation*, 43(4), 751-758. doi:10.1172/JCI104959
- Garcia-Souto, M. D. P., & Dabnichki, P. (2016). Core and local skin temperature: 3–24 months old toddlers and comparison to adults. *Building and Environment*, 104, 286-295. doi:10.1016/j.buildenv.2016.04.016
- Gardner, S. L., & Cammack, B. H. (2021). Heat Balance. In S. L. Gardner (Ed.), *Merenstein & Gardner's Handbook of Neonatal Intensive Care, Ninth Edition* (9th ed., pp. 137-164). St. Louis, Missouri: Elsevier Inc.
- GE. (2017). Panda™ and Giraffe™ Warmers service manual. In G. E. Company (Ed.). USA.
- Global, L., GOGLA, & ESMAP. (2020). Off-Grid Solar Market Trends Report 2020. Retrieved from https://www.lightingglobal.org/wp-content/uploads/2020/03/VIVID%20OCA_2020_Off_Grid_Solar_Market_Trends_Report_Full_High.pdf
- Graham, C., Lynch, G. P., English, T., Hospers, L., & Jay, O. (2021). Optimal break structures and cooling strategies to mitigate heat stress during a Rugby League

- match simulation. *Journal of Science and Medicine in Sport*, 24(8), 793-799. doi:10.1016/j.jsams.2021.04.013
- Green, A. C., Wallingford, S. C., & McBride, P. (2011). Childhood exposure to ultraviolet radiation and harmful skin effects: Epidemiological evidence. *Progress in Biophysics and Molecular Biology*, 107(3), 349-355. doi:10.1016/j.pbiomolbio.2011.08.010
- Grundstein, A., Duzinski, S., & Null, J. (2015). Impact of dangerous microclimate conditions within an enclosed vehicle on pediatric thermoregulation. *Theoretical and Applied Climatology*, 127(1-2), 103-110. doi:10.1007/s00704-015-1636-2
- Grundstein, A. J., Duzinski, S. V., Dolinak, D., Null, J., & Iyer, S. S. (2015). Evaluating infant core temperature response in a hot car using a heat balance model. *Forensic Science, Medicine and Pathology*, 11(1), 13-19. doi:10.1007/s12024-014-9619-7
- Gunga, H.-C. (2021). Desert and tropical environments. In H.-C. Gunga (Ed.), *Human Physiology in Extreme Environments* (Second edition. ed., pp. 169-221). London, England: Academic Press.
- Guntheroth, W. G., & Spiers, P. S. (2001). Thermal Stress in Sudden Infant Death: Is There an Ambiguity with the Rebreathing Hypothesis? *Pediatrics*, 107(4), 693-698. doi:10.1542/peds.107.4.693
- Hackman, P. (2001). Recognizing and Understanding the Cold-Stressed Term Infant. *Neonatal Network*, 20(8), 35-41. doi:10.1891/0730-0832.20.8.35
- Hall, J. E. (2016). *Guyton and Hall Textbook of medical physiology* (13th ed.). Philadelphia, PA: Elsevier.
- Hammarlund, K., Nilsson, G. E., öBerg, P. Å., & Sedin, G. (1980). Transepidermal water loss in newborn infants: V. Evaporation from the skin and heat exchange during the first hours of life. *Acta Paediatrica*, 69(3), 385-392. doi:10.1111/j.1651-2227.1980.tb07097.x
- Hammel, H. T., Jackson, D. C., Stolwijk, J. A., Hardy, J. D., & Stromme, S. B. (1963). Temperature Regulation By Hypothalamic Proportional Control With An Adjustable Set Point. *Journal of Applied Physiology*, 18, 1146-1154.
- Hannam, P. (2022). Australia matches its hottest day on record as Western Australia town hits 50.7C. Retrieved from <https://www.theguardian.com/australia-news/2022/jan/13/hottest-day-on-record-in-parts-of-western-australia-as->

- Hannenbergh, A. A., & Sessler, D. I. (2008). Improving perioperative temperature management. *Anesthesia and Analgesia*, 107(5), 1454-1457. doi:10.1213/ane.0b013e318181f6f2
- Harpin, V., Chellappah, G., & Rutter, N. (1983). Responses of the newborn infant to overheating. *Biology of the Neonate*, 44(2), 65-75. doi:/10.1159/000241698
- Hey, E. N., & Katz, G. (1970). The Range of Thermal Insulation in the Tissues of the Newborn Baby. *Journal of Physiology*, 207, 667-681.
- Holmberg, H. (2014). Swedes risk infants' lives by covering up prams. *The Local*. Retrieved from <https://www.thelocal.se/20140711/swedes-risk-infants-lives-by-covering-up-prams>
- Holtzclaw, B. J. (1993). Monitoring body temperature. *AACN Clinical Issues in Critical Care Nursing*, 4(1), 44-55.
- Horrow, J. C., & Rosenberg, H. (1988). Does urinary catheter temperature reflect core temperature during cardiac surgery? *Anesthesiology*, 69(6), 986-989.
- Hospers, L., Smallcombe, J. W., Morris, N. B., Capon, A., & Jay, O. (2020). Electric fans: A potential stay-at-home cooling strategy during the COVID-19 pandemic this summer? *Science of the Total Environment*, 747, 141180. doi:10.1016/j.scitotenv.2020.141180
- Hunter New England Local Health District. (2015). Local Guidelines: Thermoregulation of the neonate in NICU. John Hunter Children's Hospital: New South Wales Health, Australia
- Inge, P., Orchard, J. J., Purdue, R., & Orchard, J. W. (2022). Exercise after pregnancy. *Australian Journal of General Practice*, 51(3), 117-121. doi:https://doi.org/10.31128/AJGP-09-21-6181
- Inoue, Y., Kuwahara, T., & Araki, T. (2004). Maturation-and aging-related changes in heat loss effector function. *Journal of Physiological Anthropology and Applied Human Science*, 23(6), 289-294. doi:https://doi.org/10.2114/jpa.23.289
- Jay, O., Capon, A., Berry, P., Broderick, C., de Dear, R., Havenith, G., . . . Ebi, K. L. (2021). Reducing the health effects of hot weather and heat extremes: from personal cooling strategies to green cities. *The Lancet (British edition)*, 398(10301), 709-724. doi:10.1016/S0140-6736(21)01209-5

- Jay, O., Cramer, M. N., Ravanelli, N. M., & Hodder, S. G. (2015). Should electric fans be used during a heat wave? *Applied Ergonomics*, 46, 137-143. doi:<https://doi.org/10.1016/j.apergo.2014.07.013>
- Jay, O., Molgat-Seon, Y., Chou, S., & Murto, K. (2013). Skin temperature over the carotid artery provides an accurate noninvasive estimation of core temperature in infants and young children during general anesthesia. *Paediatric Anaesthesia*, 23(12), 1109-1116. doi:10.1111/pan.12262
- Jirapaet, V., & Jirapaet, K. (2000). Comparisons of tympanic membrane, abdominal skin, axillary, and rectal temperature measurements in term and preterm neonates. *Nursing & Health Sciences*, 2(1), 1-8. doi:10.1046/j.1442-2018.2000.00034.x
- Joseph, R. A., Derstine, S., & Killian, M. (2017). Ideal Site for Skin Temperature Probe Placement on Infants in the NICU: A Review of Literature. *Advances in Neonatal Care*, 17(2), 114-122. doi:10.1097/ANC.0000000000000369
- Kelleher, M. M., O'Carroll, M., Gallagher, A., Murray, D. M., Dunn Galvin, A., Irvine, A. D., & Hourihane, J. O. B. (2013). Newborn Transepidermal Water Loss Values: A Reference Dataset. *Pediatric Dermatology*, 30(6), 712-716. doi:10.1111/pde.12106
- Kenny, G. P., & Jay, O. (2013). Thermometry, Calorimetry, and Mean Body Temperature during Heat Stress. *Comprehensive Physiology*, 3(4), 1689-1719. doi:10.1002/cphy.c130011
- Kimberger, O., Thell, R., Schuh, M., Koch, J., Sessler, D. I., & Kurz, A. (2009). Accuracy and precision of a novel non-invasive core thermometer. *British Journal of Anaesthesia*, 103(2), 226-231. doi:10.1093/bja/aep134
- Klein, A. D., & Scammon, R. E. (1930). The regional growth in surface area of the human body in prenatal life. *Experimental Biology and Medicine*, 27, 463-466.
- Knobel, R. B. (2014). Fetal and Neonatal Thermal Physiology. *Newborn and Infant Nursing Reviews*, 14(2), 45-49. doi:10.1053/j.nainr.2014.03.003
- Ko, H. K., Flemmer, A., Haberl, C., & Simbruner, G. (2001). Methodological investigation of measuring nasopharyngeal temperature as noninvasive brain temperature analogue in the neonate. *Intensive Care Medicine*, 27(4), 736-742.
- Kumar, P. A., & Arora, H. (2006). Potential aspiration hazard when using a nasopharyngeal temperature probe with disposable cover. *Journal of Clinical Anesthesia*, 18(7), 556-557. doi:<https://doi.org/10.1016/j.jclinane.2006.05.012>

- Lahana, A., Delanaud, S., Erbani, R., Glusko-Charlet, A., Durand, E., Haraux, E., . . . Tourneux, P. (2018). Warming the premature infant in the delivery room: Quantification of the risk of hyperthermia. *Medical Engineering & Physics*, 59, 70-74. doi:10.1016/j.medengphy.2018.06.002
- Lambe, G. F., Driver, C. P., Morton, S., & Turnock, R. R. (2000). Fissurectomy as a treatment for anal fissures in children. *The Annals of the Royal College of Surgeons of England*, 82(4), 254-257.
- Laptook, A. R., Salhab, W., Bhaskar, B., & Neonatal Research, N. (2007). Admission Temperature of Low Birth Weight Infants: Predictors and Associated Morbidities. *Pediatrics*, 119(3), e643. doi:10.1542/peds.2006-0943
- Laptook, A. R., & Watkinson, M. (2008). Temperature management in the delivery room. *Seminars in Fetal and Neonatal Medicine*, 13(6), 383-391. doi:10.1016/j.siny.2008.04.003
- LeBlanc, M. H. (1991). Thermoregulation: Incubators, Radiant Warmers, Artificial Skins, and Body Hoods. *Clinics in Perinatology*, 18(3), 403-422. doi:https://doi.org/10.1016/S0095-5108(18)30505-0
- Leick-Rude, M. K., & Bloom, L. F. (1998). A comparison of temperature-taking methods in neonates. *Neonatal Network*, 17(5), 21-37.
- Li, X., Javed, M., Guo, Y., Luo, M., Cai, Z., & Xu, B. (2021). Superabsorbent Fabric Based on Weft-Back Weave Structure for Efficient Evaporative Cooling. *Advanced Materials Interfaces*, 8(1), 2001329-n/a. doi:10.1002/admi.202001329
- The Local SE. Swedes risk infants' lives by covering up prams. (2014). Retrieved from <https://www.thelocal.se/20140711/swedes-risk-infants-lives-by-covering-up-prams>
- Lund, C. (2014). Medical Adhesives in the NICU. *Newborn and Infant Nursing Reviews*, 14(4), 160-165. doi:https://doi.org/10.1053/j.nainr.2014.10.001
- Lunze, K., Bloom, D. E., Jamison, D. T., & Hamer, D. H. (2013). The global burden of neonatal hypothermia: systematic review of a major challenge for newborn survival. *BMC Medicine*, 11(1), 24-24. doi:10.1186/1741-7015-11-24
- Lynch, G. P., Periard, J. D., Pluim, B. M., Brotherhood, J. R., & Jay, O. (2018). Optimal cooling strategies for players in Australian Tennis Open conditions. *Journal of Science and Medicine in Sport*, 21(3), 232-237. doi:10.1016/j.jsams.2017.05.017

- Mance, M. J. (2008). Keeping infants warm: Challenges of hypothermia. *Advances in Neonatal Care*, 8(1), 6-12.
- Mancini, A. J. (2004). *Skin*. *Pediatrics*, 113(4), 1114-1119.
- Matsukawa, T., Sessler, D. I., Ozaki, M., Hanagata, K., Iwashita, H., & Kumazawa, T. (1997). Comparison of distal oesophageal temperature with deep and tracheal temperatures. *Canadian Journal of Anesthesia*, 44(4), 433-438. doi:10.1007/bf03014466
- Matsukawa, T., Sessler, Daniel I., Sessler, Andrew M., Schroeder, M., Ozaki, M., Kurz, A., & Cheng, C. (1995). Heat Flow and Distribution during Induction of General Anesthesia. *Anesthesiology*, 82(3), 662-673. doi:10.1097/00000542-199503000-00008 %J *Anesthesiology*
- Maxton, F. J., Justin, L., & Gillies, D. (2004). Estimating core temperature in infants and children after cardiac surgery: a comparison of six methods. *Journal of Advanced Nursing*, 45(2), 214-222. doi:2883 [pii]
- Mazumder, S., & Modest Michael, F. (2022). *Fundamentals of Thermal Radiation*. In *Radiative Heat Transfer* (4th Edition ed.): Elsevier.
- McKimmie, M. (2012). Babies at risk from covered prams Retrieved from health.thewest.com.au/news/115/babies-at-risk-from-covered-prams
- McLaren, C., Null, J., & Quinn, J. (2005). Heat stress from enclosed vehicles: moderate ambient temperatures cause significant temperature rise in enclosed vehicles. *Pediatrics*, 116(1), e109-112. doi:10.1542/peds.2004-2368
- Mekjavic, I. B., & Rempel, M. E. (1990). Determination of esophageal probe insertion length based on standing and sitting height. *Journal of Applied Physiology*, 69(1), 376-379.
- Merklin, R. J. (1974). Growth and distribution of human fetal brown fat. *The Anatomical Record*, 178(3), 637-645. doi:10.1002/ar.1091780311
- Mitchell, J. B., McFarlin, B. K., & Dugas, J. P. (2003). The Effect of Pre-Exercise Cooling on High Intensity Running Performance in the Heat. *International Journal of Sports Medicine*, 24(2), 118-124. doi:10.1055/s-2003-38203
- Moise, A. F., Gies, H. P., & Harrison, S. L. (1999). Estimation of the annual solar UVR exposure dose of infants and small children in tropical Queensland, Australia. *Photochemistry and Photobiology*, 69(4), 457-463.

- Molgat-Seon, Y., Daboval, T., Chou, S., & Jay, O. (2013). Accidental overheating of a newborn under an infant radiant warmer: a lesson for future use. *Journal of Perinatology*, 33(9), 738-739. doi:10.1038/jp.2013.32
- Molgat-Seon, Y., Daboval, T., Chou, S., & Jay, O. (2014). Assessing neonatal heat balance and physiological strain in newborn infants nursed under radiant warmers in intensive care with fentanyl sedation. *European Journal of Applied Physiology*, 114(12), 2539-2549. doi:10.1007/s00421-014-2964-0
- Morris, N. B., Chaseling, G. K., English, T., Gruss, F., Maideen, M. F. B., Capon, A., & Jay, O. (2021). Electric fan use for cooling during hot weather: a biophysical modelling study. *The Lancet: Planetary Health*, 5(6), e368-e377. doi:10.1016/S2542-5196(21)00136-4
- Morris, N. B., Gruss, F., Lempert, S., English, T., Hospers, L., Capon, A., & Jay, O. (2019). A Preliminary Study of the Effect of Dousing and Foot Immersion on Cardiovascular and Thermal Responses to Extreme Heat. *JAMA: The Journal of the American Medical Association*, 322(14), 1411-1413. doi:10.1001/jama.2019.13051
- Narendran, V., & Hoath, S. B. (1999). Thermal management of the low birth weight infant: A cornerstone of neonatology. *The Journal of Pediatrics*, 134(5), 529-531. doi:10.1016/S0022-3476(99)70232-5
- National Health Service (NHS). Keeping your baby safe in the sun. (2021). Retrieved from <https://www.nhs.uk/conditions/baby/first-aid-and-safety/safety/safety-in-the-sun/>
- Neubeck, S., & Hansen, R. D. (1998). Tympanic thermometers: how accurate? *Nursing* 98, [Suppl].
- Nicholls, L., & Strengers, Y. (2018). Heatwaves, cooling and young children at home: Integrating energy and health objectives. *Energy Research & Social Science*, 39, 1-9. doi:10.1016/j.erss.2017.10.002
- Nikolovski, J., Stamatas, G. N., Kollias, N., & Wiegand, B. C. (2008). Barrier Function and Water-Holding and Transport Properties of Infant Stratum Corneum Are Different from Adult and Continue to Develop through the First Year of Life. *Journal of Investigative Dermatology*, 128(7), 1728-1736. doi:https://doi.org/10.1038/sj.jid.5701239
- NSW Health. Babies and children in the heat. (2022). Retrieved from

<https://www.health.nsw.gov.au/environment/beattheheat/Pages/babies-children-hot-weather.aspx>

- O'Callaghan, P. W., & Probert, S. D. (1976). Thermal insulation provided by dry, single-layer clothing materials. *Applied Energy*, 2(4), 269-277. doi:10.1016/0306-2619(76)90013-1
- O'Toole, S. (1998). Temperature measurement devices. *Professional Nurse*, 13(11), 779-784, 786.
- O'Grady, N. P., Barie, P. S., Bartlett, J. G., Bleck, T., Carroll, K., Kalil, A. C., . . . Masur, H. (2008). Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. 36(4), 1330-1349. doi:10.1097/CCM.0b013e318169eda9
- Olsen, I. E., Lawson, M. L., Meinen-Derr, J., Sapsford, A. L., Schibler, K. R., Donovan, E. F., & Morrow, A. L. (2009). Use of a Body Proportionality Index for Growth Assessment of Preterm Infants. *The Journal of Pediatrics*, 154(4), 486-491. doi:<https://doi.org/10.1016/j.jpeds.2008.10.012>
- Parsons, K. C. (2003). *Human Thermal Environments* (2nd ed.). London: Taylor & Francis.
- Parsons, K. C. (2015). *Human Thermal Environments: The Effects of Hot, Moderate, and Cold Environments on Human Health, Comfort, and Performance*, Third Edition (3rd ed. ed.). Hoboken: CRC Press.
- Payton, M. (2016). Parents placing a blanket over baby's pram in hot weather 'put their children at risk'. Retrieved from <https://www.independent.co.uk/life-style/health-and-families/health-news/uk-heat-sun-pram-stroller-parents-blanket-over-baby-pram-in-hot-weather-put-their-children-at-risk-a7145311.html>
- Polin, R. A. (2021). *Fetal and Neonatal Physiology* (Sixth edition. ed.). Philadelphia, Pennsylvania: Elsevier.
- Pomerance, J. J., Madore, C., & Gluck, L. (1974). Effect of temperature on survival of infants with RDS. *Pediatric Research*, 8(4), 449-449. doi:10.1203/00006450-197404000-00656
- Raone, B., Raboni, R., Rizzo, N., Simonazzi, G., & Patrizi, A. (2014). Transepidermal Water Loss in Newborns Within the First 24 Hours of Life: Baseline Values and Comparison with Adults. *Pediatric Dermatology*, 31(2), 191-195.

doi:10.1111/pde.12274

- Ravanelli, N. M., Hodder, S. G., Havenith, G., & Jay, O. (2015). Heart rate and body temperature responses to extreme heat and humidity with and without electric fans. *JAMA : The Journal of the American Medical Association*, 313(7), 724-725. doi:<https://doi-org.ezproxy.library.sydney.edu.au/10.1001/jama.2015.153>
- Roberts, A. E., Allanson, J. E., Tartaglia, M., & Gelb, B. D. (2013). Noonan syndrome. *The Lancet*, 381(9863), 333-342. doi:[https://doi.org/10.1016/S0140-6736\(12\)61023-X](https://doi.org/10.1016/S0140-6736(12)61023-X)
- Romanovsky, A. A. (2014). Skin temperature: its role in thermoregulation. *Acta Physiologica*, 210(3), 498-507. doi:10.1111/apha.12231
- Rotello, L. C., Crawford, L., & Terndrup, T. E. (1996). Comparison of infrared ear thermometer derived and equilibrated rectal temperatures in estimating pulmonary artery temperatures. *Critical Care Medicine*, 24(9), 1501-1506. doi:10.1097/00003246-199609000-00012
- Rutter, N., & Hull, D. (1979). Response of term babies to a warm environment. *Archives of Disease in Childhood*, 54(3), 178-183. doi:10.1136/ad.54.3.178
- Sahiledengle, B., Tekalegn, Y., Zenbaba, D., Woldeyohannes, D., & Teferu, Z. (2020). Which Factors Predict Hospital Length-of-Stay for Children Admitted to the Neonatal Intensive Care Unit and Pediatric Ward? A Hospital-Based Prospective Study. *Global Pediatric Health*, 7, 2333794x20968715. doi:10.1177/2333794x20968715
- Sauer, P. J., Dane, H. J., & Visser, H. K. (1984). New standards for neutral thermal environment of healthy very low birthweight infants in week one of life. *Archives of Disease in Childhood*, 59(1), 18-22. doi:10.1136/ad.59.1.18
- Scipioni, M., Silva, E., & Farahi, F. (2020). Solar Absorption Index (SAI) as a Parameter to Assess the Coolness of Fabrics Exposed to Sunlight. *Fibres and Textiles in Eastern Europe*, 28(5(143)), 44-49. doi:10.5604/01.3001.0014.2383
- Sedin, G., Hammarlund, K., Nilsson, G. E., Strömberg, B., & Öberg, P. Å. (1985). Measurements of Transepidermal Water Loss on Newborn Infants. *Clinics in Perinatology*, 12(1), 79-99. doi:10.1016/S0095-5108(18)30886-8
- Sehat, A. R., Nirmal, U., & Jin, Z. (2017). State of the art baby strollers: Design review and the innovations of an ergonomic baby stroller. *Cogent Engineering*, 4(1). doi:10.1080/23311916.2017.1333273

- Sessler, D. (2008). Temperature Monitoring and Perioperative Thermoregulation. *Anesthesiology*, 109(2), 318-338. doi:10.1097/ALN.0b013e31817f6d76
- Silverman, W. A., Fertig, J. W., & Berger, A. P. (1958). The influence of the thermal environment upon the survival of newly born premature infants. *Pediatrics*, 22(5), 876-886.
- Sinclair, J. C., & Sinclair, J. C. (2002). Servo-control for maintaining abdominal skin temperature at 36C in low birth weight infants. *Cochrane Library*, 2010(1). doi:10.1002/14651858.CD001074
- Sinha, P. K., Kaushik, S., & Neema, P. K. (2004). Massive epistaxis after nasopharyngeal temperature probe insertion after cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia*, 18(1), 123-124. doi:10.1053/j.jvca.2003.10.030
- Slaton, J. (2023). Best stroller fans. Retrieved from https://www.babycenter.com/baby-products/strollers-and-travel-systems/best-stroller-fans_40009180
- Snellen, J. W. (1960). External work in level and grade walking on a motor-driven treadmill. *Journal of Applied Physiology*, 15(5), 759-763. doi:10.1152/jappl.1960.15.5.759
- Song, W., Wang, F., & Zhang, C. (2019). Intermittent wetting clothing as a cooling strategy for body heat strain alleviation of vulnerable populations during a severe heatwave incident. *Journal of Thermal Biology*, 79, 33-41. doi:10.1016/j.jtherbio.2018.11.012
- Stoen, R., & Sessler, D. I. (1990). The thermoregulatory threshold is inversely proportional to isoflurane concentration. *Anesthesiology*, 72(5), 822-827.
- Sulyok, E., Jéquier, E., & Prod'hom, L. S. (1973). Respiratory contribution to the thermal balance of the newborn infant under various ambient conditions. *Pediatrics* (Evanston), 51(4), 641-650. doi:https://doi.org/10.1542/peds.51.4.641
- Sund-Levander, M., Grodzinsky, E., Loyd, D., & Wahren, L. K. (2004). Errors in body temperature assessment related to individual variation, measuring technique and equipment. *International Journal of Nursing Practice*, 10(5), 216-223. DOI: 10.1111/j.1440-172X.2004.00483.x
- Sybert, V. P., & McCauley, E. (2004). Turner's Syndrome. *The New England Journal of Medicine*, 351(12), 1227-1238. doi:10.1056/NEJMra030360
- Székel, M., & Garai, J. (2018). Thermoregulation and age. *Handbook of Clinical*

- Neurology, 156, 377-395. doi:<https://doi.org/10.1016/B978-0-444-63912-7.00023-0>
- Teunissen, L. P. J., Klewer, J., de Haan, A., J.J., d. K., & Daanen, H. A. M. (2011). Non-invasive continuous core temperature measurement by zero heat flux. *Physiological Measurement*, 32, 559-570. doi:10.1088/0967-3334/32/5/005
- The Children's Hospital at Westmead. (2021). *Thermoregulation in Neonatal Care.*: Sydney Children's Hospital Network, Australia
- The Royal Children's Hospital Melbourne. (2020). *Assisted Thermoregulation. Clinical Guidelines (Nursing).* Retrieved from https://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Thermoregulation_in_the_Preterm_Infant/#management
- theglobaleconomy.com. (2023). Birth rate - Country rankings. Retrieved from https://www.theglobaleconomy.com/rankings/birth_rate/#:~:text=The%20average%20for%202021%20based,countries%20where%20data%20are%20available
- Togwa, T., Nemoto, T., Yamazaki, T., & Kobayashi, T. (1976). A modified internal temperature measurement device. *Medical & Biological Engineering*, 14(3), 361-364. doi:10.1007/BF02478138
- van der Spek, R. D., van Lingen, R. A., & van Zoeren-Grobbe, D. (2009). Body temperature measurement in VLBW infants by continuous skin measurement is a good or even better alternative than continuous rectal measurement. *Acta Paediatrica*, 98(2), 282-285. doi:10.1111/j.1651-2227.2008.01063.x
- Vanos, J. K., Middel, A., Poletti, M. N., & Selover, N. J. (2018). Evaluating the impact of solar radiation on pediatric heat balance within enclosed, hot vehicles. *Temperature*, 5(3), 276-292. doi:10.1080/23328940.2018.1468205
- Visscher, M., & Narendran, V. (2014). Neonatal Infant Skin: Development, Structure and Function. *Newborn and Infant Nursing Reviews*, 14(4), 135-141. doi:10.1053/j.nainr.2014.10.004
- Vohra, S., Roberts, R. S., Zhang, B., Janes, M., & Schmidt, B. (2004). Heat Loss Prevention (HeLP) in the delivery room: A randomized controlled trial of polyethylene occlusive skin wrapping in very preterm infants. *The Journal of Pediatrics*, 145(6), 750-753. doi:10.1016/j.jpeds.2004.07.036
- Wailoo, M. P., Petersen, S. A., & Whitaker, H. (1990). Disturbed nights and 3-4 month old

- infants: the effects of feeding and thermal environment. *Archives of Disease in Childhood*, 65(5), 499-501. doi:10.1136/ad.65.5.499
- Waldron, S., & MacKinnon, R. (2007). Neonatal Thermoregulation. *Infant*, 3(3), 101-104.
- Watkinson, M. (2006). Temperature control of premature infants in the delivery room. *Clinics in Perinatology*, 33(1), 43-53. doi:10.1016/j.clp.2005.11.018
- Wenger, C. B. (1972). Heat of evaporation of sweat: thermodynamic considerations. *Journal of Applied Physiology*, 32(4), 456-459. doi:10.1152/jappl.1972.32.4.456
- Wheldon, A. E., & Rutter, N. (1982). The heat balance of small babies nursed in incubators and under radiant warmers. *Early Human Development*, 6, 131-143.
- WHO. (1997). Thermal Protection of the Newborn: a practical guide. (WHO/RHT/MSM/97.2). Geneva: World Health Organisation.
- Wilson, L. (2008). Discussion paper: The great pram cover-up-a cautionary tale. *Neonatal, Paediatric and Child Health Nursing*, 11(1), 26-28.
- Wilson, L., Quine, S., & Lewis, M. (2010). Hiding under the blankets: reasons why parents cover infants' strollers and prams. *Neonatal, Paediatric, and Child Health Nursing*, 13(2), 13-17.
- World Health Organisation. (2015). WHO recommendations on interventions to improve preterm birth outcomes. Geneva: World Health Organisation.
- Yamakage, M., & Namiki, A. (2003). Deep temperature monitoring using a zero-heat-flow method. *Journal of Anesthesia*, 17, 108-115. doi:10.1007/s005400300026

APPENDIX A

Attestation Statement for Chapter 3

Faculty of Medicine and Health

Author Contribution Statement

Candidate Name: Mohammad Fauzan Bin Maideen

Degree Title: Doctor of Philosophy (PhD)

Paper Title: An assessment of skin temperature over the carotid artery as a non-invasive core temperature monitoring site in premature infants under radiant warmers.

As the corresponding author of the above paper, I confirm that the above candidate has made the following contributions:

- Conception and design of the research
- Collection of data
- Analysis and interpretation of the findings
- Writing the paper and critical appraisal of content

Signed: OLLIE JAY

Name: OLLIE JAY

Date: 30-Jun-2023

As the first author of the above paper, I confirm that I have made the following contributions:

- Conception and design of the research
- Collection of data
- Analysis and interpretation of the findings
- Writing the paper and critical appraisal of content

Signed: Mohammad Fauzan
Bin Maideen

Name: Mohammad Fauzan Bin Maideen

Date: 30-Jun-2023

APPENDIX B

Attestation Statement for Chapter 5

Faculty of Medicine and Health

Author Contribution Statement

Candidate Name: Mohammad Fauzan Bin Maideen

Degree Title: Doctor of Philosophy (PhD)

Paper Title: An evaluation of skin contact temperature as a non-invasive method for monitoring core temperature in premature infants under radiant warmers.

As the corresponding author of the above paper, I confirm that the above candidate has made the following contributions:

- Conception and design of the research
- Collection of data
- Analysis and interpretation of the findings
- Writing the paper and critical appraisal of content

Signed: OLLIE JAY

Name: OLLIE JAY

Date: 30-Jun-2023

As the first author of the above paper, I confirm that I have made the following contributions:

- Conception and design of the research
- Collection of data
- Analysis and interpretation of the findings
- Writing the paper and critical appraisal of content

Signed: Mohammad Fauzan
Bin Maideen

Name: Mohammad Fauzan Bin Maideen

Date: 30-Jun-2023

APPENDIX C

Attestation Statement for Chapter 7

Faculty of Medicine and Health

Author Contribution Statement

Candidate Name: Mohammad Fauzan Bin Maideen

Degree Title: Doctor of Philosophy (PhD)

Paper Title: Optimal low-cost cooling strategies for infant strollers during hot weather.

As the corresponding author of the above paper, I confirm that the above candidate has made the following contributions:

- Conception and design of the research
- Collection of data
- Analysis and interpretation of the findings
- Writing the paper and critical appraisal of content

Signed: OLLIE JAY

Name: OLLIE JAY

Date: 30-Jun-2023

As the first author of the above paper, I confirm that I have made the following contributions:

- Conception and design of the research
- Collection of data
- Analysis and interpretation of the findings
- Writing the paper and critical appraisal of content

Signed: Mohammad Fauzan
Bin Maideen

Name: Mohammad Fauzan Bin Maideen

Date: 30-Jun-2023

APPENDIX D:

Ethical Approval for Experimental Study One and Two



Health
Nepean Blue Mountains
Local Health District

NBMLHD Human Research Ethics Office

Level 5 South Block
Nepean Hospital
Kingswood NSW 2747
Telephone: (02) 4734 3441
Facsimile: 4734 1365
Email: NBMLHD-ResearchOffice@health.nsw.gov.au

**NEPEAN BLUE MOUNTAINS LOCAL HEALTH DISTRICT HUMAN RESEARCH ETHICS COMMITTEE
CERTIFICATE OF APPROVAL**

Wednesday, 12 April 2017

Professor Ralph Nanan
Department of Paediatrics
Level 5 South Block
Nepean Hospital

Dear Professor Nanan,

Project No: HREC/17/NEPEAN/06

Project Title: Monitoring and Regulating Neonatal Heat Balance under Radiant Warmers

Principal Investigator: Professor Ralph Nanan

Your request to undertake the above protocol was considered by the NBMLHD Human Research Ethics Committee (HREC) at its meeting held on the 28/2/2017.

*On receipt of your response dated 7/4/2017 to the concerns of the Committee dated 22/3/2017, we are satisfied that your protocol meets the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was **APPROVED on 11/4/2017 to be conducted as a Single Site study.***

It is the Principal Investigator's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principle Researcher is required to note the following conditions of approval:

- The coordinating investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.
- The coordinating investigator will immediately report any protocol deviation / violation, together with details of the procedure put in place to ensure the deviation / violation does not recur.
- The Coordinating Investigator will provide to the HREC in the specified format proposed amendments to the protocol or conduct of the research which may affect the ethical acceptability of the project. Copies of all proposed changes when approved by the HREC must also be provided to the research governance officer.
- The HREC must be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.
- The Coordinating Chief Investigator must provide an annual report to the HREC and a final report at completion of the study, in the specified format. HREC approval is granted for a period of 5 years and ongoing approval is contingent upon annual report submission. Annual Reports for all studies should be submitted on the anniversary of the approval date of project. They will be processed and presented to the HREC at the next scheduled meeting. A copy of the Annual / Final Research Report Form can be obtained electronically from the Research Office on request.
- It should be noted that compliance with the ethical guidelines is entirely the responsibility of the investigators.

HREC/17/NEPEAN/06 – Cont'd

- The HREC has the discretion to adopt other appropriate mechanism for monitoring depending on the complexity, design and risk perceived, including:
 - Discussion of relevant aspects of the project with investigators at any time.
 - Random inspection of research sites, data or consent
 - Interview with research participants or other formats of feedback from them.
 - Request and review reports from independent agencies such as Data and Safety Monitoring Board.
- For clinical trials using implantable medical devices, the coordinating investigator will confirm to the HREC that a process has been established for tracking participants with consent for the lifetime of the device and will immediately report any device incidents to the Therapeutic Goods Administration (TGA).
- If your research project is an interventional trial please ensure you register your trial onto one of the clinical trial registries, for example. <http://www.anzctr.org.au/>

The NBMLHD HREC has been accredited by the NSW Ministry of Health as a lead HREC to provide the single ethical and scientific review of proposals to conduct research within the NSW public health system. This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*

SPECIAL CONDITIONS: N/A

N/A

Approved Documents:

Documents reviewed and approved at the meeting were:

Document	Version	Date
NEAF Submission code AU/	AU/1/E45B28	-
Protocol	Version 2.0	7/4/2017
Participant Information Sheet and Consent Form	Version 2.0	7/4/2017
Brochure for Parents and Guardians	Version 2.0	7/4/2017
Technical description for the Radiant Warmer Clinical Study		9 January 2017
ARTG Certificate		3/2/2010
Certificate for inclusion of a medical device TGA		25/2/2007

Approved Sites:

Approval is given for this research project to be conducted at the following sites and campuses:

- Nepean Hospital NICU – By Professor Nanan

HREC/17/NEPEAN/06 – Cont'd

RESEARCH GOVERNANCE - Site-Specific Assessment (SSA):

SSA authorisation is required at all sites participating in the study. SSA must be authorised at a site before the research project can commence via the Chief Executive or their delegate – the Research Governance Officer.

The completed Site-Specific Assessment Form as well as a copy of this ethics approval letter and all approved documents must be submitted to the Research Governance Officer for authorisation by the Chief Executive or delegate. This applies to each site participating in the research.

Yours Sincerely,



Dr. Jamshid Kalantar
Chair, Human Research Ethics Committee
Nepean Blue Mountains LHD

Cc: Gina Oliver Research Governance

Please quote project number and title in all correspondence



Health
Nepean Blue Mountains
Local Health District

NBMLHD Research Governance Office

Telephone: (02) 4734 1998
Facsimile: 4734 1967
Email: NBMLHD-RGO@health.nsw.gov.au

TRIM Ref: NBM

29 May 2017

Professor Ralph Nanan
Department of Paediatrics
Level 5, South Block,
Nepean Hospital

Dear Professor Nanan,

HREC reference number: hrec/17/nepean/6
SSA reference number: SSA/17/NEPEAN/52
Project title: Neonatal Heat Balance
Protocol number: Version 3 dated 15 May 2017

Thank you for submitting an application for authorisation of this project.

I am pleased to inform you that authorisation has been granted for this study to take place at the following sites:

- Nepean Hospital
 - Neonatal Intensive Care Unit

The approved information and consent documents for use at this site are:

- Participant Information Sheet and Consent Form –Version 3 dated 15 May 2017.
- Brochure: Monitoring and regulating neonatal heat balance under radiant warmers. Version 2 dated 7 April 2017

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. All non-Nepean Blue Mountains Local Health District (NBMLHD) research team members involved in your study must complete External Researcher requirements before approval is granted for them to conduct study visits at any of the facilities across NBMLHD. **Mr Mohammad Fauzen Bin Maideen has completed these requirements.**

TOGETHER
**ACHIEVING
BETTER HEALTH**

Nepean Blue Mountains Local Health District
ABN 31 910 677 424

PO Box 63, Penrith NSW 2751
Tel (02) 4734 2000
Website www.nbmlhd.health.nsw.gov.au

2. Insurance certificate must be current for governance clearance to remain valid. The insurance certificate submitted expires **31 October 2017**. Please submit updated certificate when issued.
3. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and which are submitted to the lead HREC for review, are copied to the research governance officer;
4. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project, are to be submitted to the research governance officer.

I wish you every success in your research.

Yours sincerely,



✓ Gina Oliver
NBMLHD - Research Governance Officer

cc: NBMLHD HREC



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

ARTG Certificate

Issued to

GE Healthcare Australia Pty Ltd

for approval to supply

GE Healthcare Australia Pty Ltd - Warmer, radiant, infant, mobile

ARTG Identifier ARTG Start date Product Category GMDN GMDN Description Intended Purpose	168674 Class IIb 03/02/2010 Medical Device Included Class IIb 17433 Warmer, radiant, infant, mobile This infant warmer contains an infrared heating element and is intended to emit controlled evenly distributed heat to newborn and infant patients. It is intended for newborns and infants who require a thermal environment. This warmer has wheels and can be moved to different areas of the room or ward.
--	--

Manufacturer(s) Details	Address	Manufacturing steps
Olmeda Medical a Division of Datex-Ohmeda	8880 Germann Road LAUREL, MARYLAND, 20723 United States Of America	

ARTG Standard Conditions

The above Medical Device Included Class IIb has been entered on the Register subject to the following conditions:

- The automatic conditions applicable to the inclusion of all kinds of medical devices in the Register are as specified in section 41FN of the Therapeutic Goods Act 1989.
- The standard conditions that are imposed under section 41FO of the Therapeutic Goods Act 1989 when kinds of medical devices are included in the Register are as set out in the following paragraphs.
- For a medical device included in the Register under Chapter 4 and imported into Australia, the Sponsor must ensure that information about the Sponsor is provided in such a way as to allow the sponsor to be identified.
- Each sponsor shall retain records of the distribution of all of the sponsor's medical devices included in the Register under Chapter 4. In the case of records relating to a Class AIMD medical device, Class III medical device, or Class IIb medical device that is an implantable medical device, the distribution records shall be retained for a minimum period of 10 years. In the case of records relating to any other device, the distribution records shall be retained for a minimum period of 5 years.
- The sponsor of a medical device included in the Register under Chapter 4 shall keep an up to date log of information of the kind specified in Regulation 5.8.
- It is a condition of inclusion in the ARTG that the sponsor of a medical device that is an AIMD, Class III or implantable Class IIb provides three consecutive annual reports to the Head of the Office of Devices, Blood and Tissues, Therapeutic Goods Administration following inclusion of the device in the ARTG (as specified in 5.8 of the regulations). Annual reports are due on 1 October each year. Reports should be for the period 1 July to 30 June. The first report following the date of inclusion in the ARTG must be for a period of at least six months but no longer than 18 months. Subsequent reports are to be provided on 1 October for a further 2 years. The annual report must include all complaints received by the manufacturer relating to problems with the use of the device that have been received by them over the year.
- Where a medical device included in the Register, contains a substance which is included in the Fourth Schedule to the Customs (Prohibited Imports) Regulations or the Eighth Schedule to the Customs (Prohibited Exports) Regulations the Sponsor shall, at the time of importation or exportation of the medical device, be in possession of a licence and a permission for importation or exportation of each consignment of the goods as required by those regulations.
- A sponsor shall ensure that a medical device within their control is stored and transported in accordance with the instructions and information provided by the manufacturer.

Products covered by this Entry

1. Warmer, radiant, infant, mobile

Product Specific Conditions

No specific conditions have been recorded against this entry.

Product Standard Indications

No standard indications have been recorded against this entry.

Product Specific Indications

No specific indications have been recorded against this entry.

END OF CERTIFICATE

ARTG Certificate

APPENDIX E:

Public Engagement and Media Coverage Related to

Experimental Study Three

Public Engagement with The Conversation

Published on February 20, 2023

URL: <https://theconversation.com/covering-your-babys-pram-with-a-dry-cloth-can-increase-the-temperature-by-almost-4-degrees-heres-what-to-do-instead-199099>

Covering your baby's pram with a dry cloth can increase the temperature by almost 4 degrees. Here's what to do instead

THE CONVERSATION

Academic rigour, journalistic flair



Shutterstock

Covering your baby's pram with a dry cloth can increase the temperature by almost 4 degrees. Here's what to do instead

Published: February 20, 2023 12:52pm AEDT

James Smallcombe

Post-doctoral Research Associate, University of Sydney

Mohammad Fauzan Bin Maideen

Associate Lecturer in Paediatric Physiotherapy, University of Sydney

Ollie Jay

Professor of Heat & Health; Director of Heat & Health Research Incubator; Director of Thermal Ergonomics Laboratory, University of Sydney

We like to think of babies as tiny versions of ourselves. But babies aren't simply miniature adults, especially when it comes to coping in the heat. Babies are at greater risk of overheating and need different cooling strategies to those that work for adults.

Parents have long covered prams and strollers with cloth to shade the carriage from the hot sun. However, our recent study showed this can substantially increase temperatures inside the stroller.

After just 20 minutes – the time it takes to go to the shop or drop your child off at daycare – the stroller carriage was 3.7°C hotter than outside when draped with a dry flannelette cloth and 2.6°C when draped with dry muslin.

Covering your baby's pram with a dry cloth can increase the temperature by almost 4 degrees. Here's what to do instead

Attaching a battery-operated fan to the stroller wasn't very effective either at reducing the stroller temperature, cooling the carriage by just 0.1°C relative to outside.

But dampening the cloth can reduce the temperature in the carriage.

Read more: Top 10 tips to keep cool this summer while protecting your health and your budget

Why are babies vulnerable in the heat?

There are three main reasons why babies might struggle more in hot weather compared to adults.

First, their body shape is very different. Infants have a much greater area of skin surface available to exchange heat with the surrounding environment, compared to their body mass. This means in very hot conditions their body temperature can warm up at a much faster rate.



Babies can't regulate their own temperature. Shutterstock

Second, infants can't sweat as much as mum or dad and are therefore less able to cool down by sweat evaporation. This is the main physiological disadvantage that places them at greater risk in hot weather.

Finally – and possibly most importantly – babies are almost entirely dependent on someone else to keep them cool. Other than crying, babies can't communicate that they are too hot. On a hot day, it is the parents who have to check for signs of distress, choose suitable clothing, and make sure shade is found during the hottest part of the day (normally noon to 3pm). Babies can't do any of this for themselves.

Read more: Curious Kids: What happens in the body when we sweat?

So, what can be done to keep baby strollers cool?

<https://theconversation.com/covering-your-babys-pram-with-a-dry-cloth-can-increase-the-temperature-by-almost-4-degrees-heres-what-to-do-inst...> 2/4

Covering your baby's pram with a dry cloth can increase the temperature by almost 4 degrees. Here's what to do instead

In our same study, we also showed some strategies are really effective at cooling strollers down even on hot and sunny days.

Loosely draping a *damp* muslin cloth over the stroller reduced the temperature inside the stroller by 3°C.

This cooling effect was even greater when a damp cloth was combined with a clip-on fan, reducing the stroller temperature by 4.7°C compared with outside.

This method harnesses the power of evaporation. Just like we lose body heat when sweat evaporates from our skin, the evaporation of water from the damp cloth removes heat from the air inside the stroller and lowers the temperature inside.

Using a spray bottle to regularly top-up the water in the cloth every 15-20 minutes will prevent it drying out and increase the amount of time this method will provide cool relief.



Author provided

How else can I protect my baby from the heat?

Minimise the time spent outside with your infant during hot weather – get from A to B as quickly as possible.

Babies should never be left in a stationary stroller in the sun (even if covered with a damp cloth) as this reduces air movement through the stroller and increases the speed at which it heats up.

Any time infants or children are exposed to the heat, it's important to keep them well hydrated. Drinking water or breastfeeds should be offered frequently. Infants will need more fluids during hot weather.

Covering your baby's pram with a dry cloth can increase the temperature by almost 4 degrees. Here's what to do instead



Make sure babies are well hydrated when it's hot. Shutterstock

It's also important to regularly check infants for signs of heat illness. The most common are:

- being overly warm to touch
- hot, red and dry skin
- irritability
- looking generally unwell and/or lethargic.

If your baby is showing signs of heat illness, find cool relief immediately and seek medical help.

Read more: [Evacuating with a baby? Here's what to put in your emergency kit](#)

Media Coverage related to the Experimental Study Three

1. <https://www.news.com.au/lifestyle/parenting/babies/common-and-deadly-pram-mistake-aussies-are-making/news-story/9dae15a1df41edf6e08da0588e23baf0>

Common and deadly pram mistake Aussies are making

A world-first Australian study has looked at the impact of covering a pram on a hot Australian day. The results may surprise you.

Carla Mascarenhas

🕒 2 min read February 21, 2023 - 6:22PM  news.com.au

🗨️ 4 comments

2. <https://www.abc.net.au/news/2023-02-21/pram-safety-research-finds-dangers-of-coverings/101972028>

10 NEWS

Just In Watch Live Voice Referendum Politics World Business Analysis Sport Science Health Arts Fact Check Corona

Heat researchers call for Australia's pram safety guidelines to be updated after world-first study

By national education and parenting reporter Conor Duffy
Posted Tue 21 Feb 2023 at 5:43am



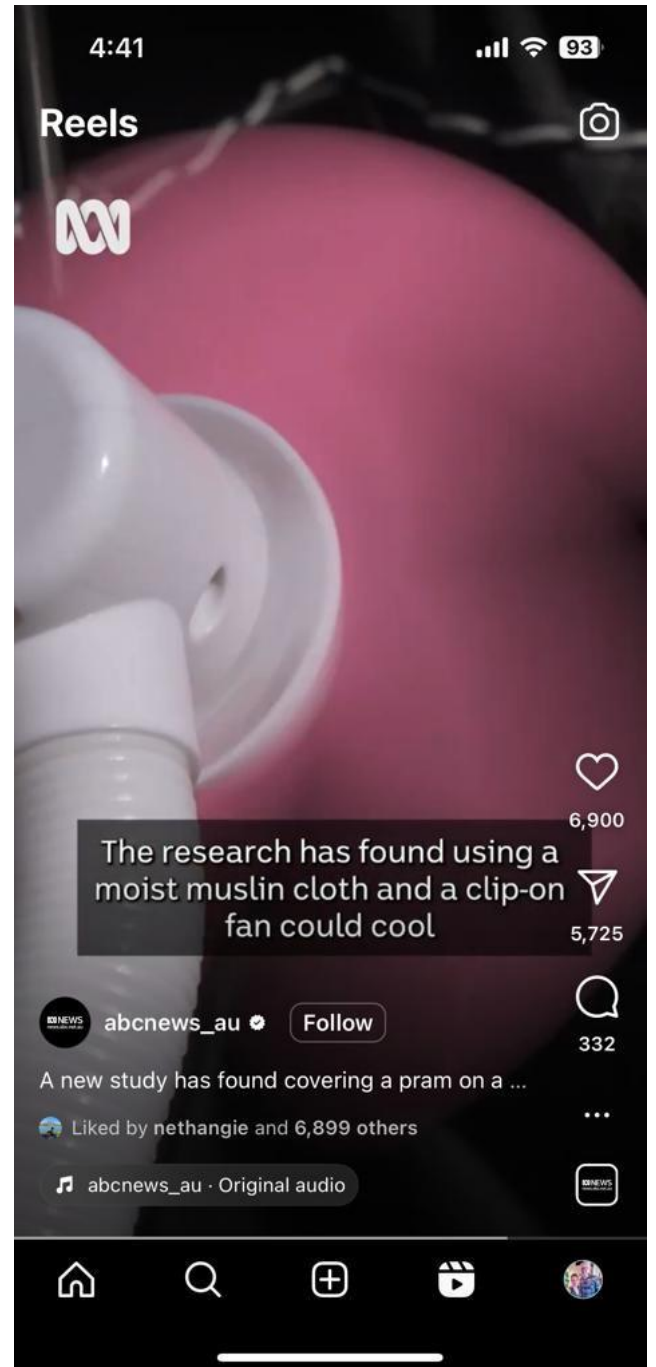
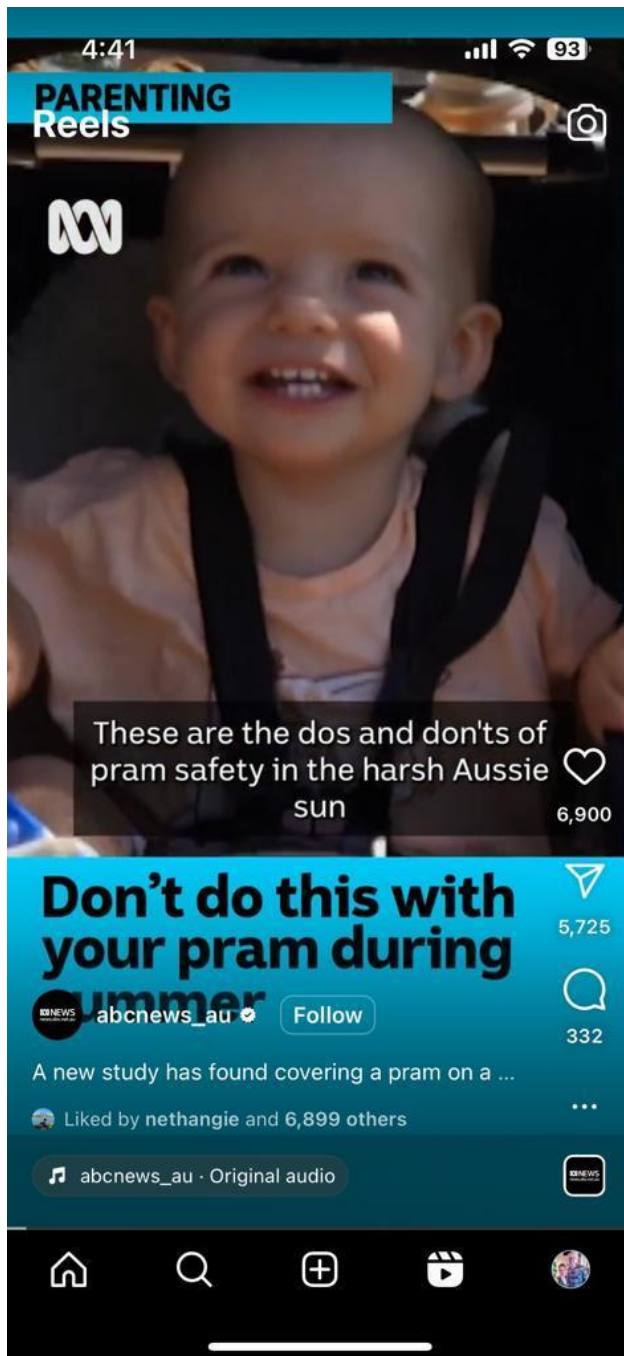
3. <https://www.9news.com.au/national/pram-safety-calls-for-australia-to-update-guidelines-after-world-first-study/2aaa4e03-e85e-456a-aff6-5a2c4e43edbf>



4. https://au.sports.yahoo.com/covering-babys-pram-dry-cloth-015255075.html?guccounter=1&guce_referrer=aHR0cHM6Ly93d3cuZ29vZ2x1LmNvbS8&guc_referrer_sig=AQAAAI08Occt826hbKdAWr644cDrI6hguogEJaxY7Rjv-p-INZBpV1xlVtRpXctbXh0wHQAcGz5c49Ega9Z0zC4kqv-cu_jSFn6EI3zlyspjJDQYpINskoPVWlFRXGMP8GT09N3irwUOTgiKI99pz-zm8_dVp4hs0FWXRtoQY3D9x3k

The screenshot shows the Yahoo! Sports website. The top navigation bar includes Sports, NRL, AFL, Tennis, Football, Rugby, Cricket, Motorsport, NBA, Fantasy, NFL, Golf, and MMA. Below this is a banner for 'FEED THEM' and 'DONATE NOW' with the SADAQA WELFARE FUND logo. A purple banner below that reads 'LOVE SPORT? Score the biggest stories of the week with our newsletter'. The article title is 'Covering your baby's pram with a dry cloth can increase the temperature by almost 4 degrees. Here's what to do instead'. The author is Ollie Jay, Professor of Heat & Health; Director of Heat & Health Research Incubator; Director of Thermal Ergonomics Laboratory, University of Sydney, James Smallcombe, Post-doctoral. The article was published on 20 February 2023 and is a 3-minute read. A SADAQA WELFARE FUND logo is visible in the bottom right corner.

5. https://www.instagram.com/reel/Co6azCEto7T/?utm_source=ig_web_copy_link&igshid=MjAxZDBhZDhlNA==



6. <https://www.sydney.edu.au/news-opinion/news/2023/02/22/parents-are-unintentionally-heating-up-prams--here-s-what-you-ne.html>



THE UNIVERSITY OF
SYDNEY

StudyResearchEngage with usAbout usNews & opinion



Home / News & opinion / News / 2023: all news / February / Parents are unintentionally heating up prams: here's what you need to know

← Home

← News & opinion

News

2023: all news

Arts & culture

Business & economics

News_

Parents are unintentionally heating up prams: here's what you need to know

22 February 2023

How to protect infants from heat stress when out and about

A University of Sydney study finds common strategies used to protect infants from the heat can warm up a pram by almost 4

Read the study

Share

APPENDIX F:
Publications Written During the Doctoral Candidature,
Yet Not Related To, Nor Formally Included
Within This Thesis

Electric fan use for cooling during hot weather: a biophysical modelling study

Nathan B Morris, Georgia K Chaseling, Timothy English, Fabian Gruss, Mohammad Fauzan Bin Maideen, Anthony Capon, Ollie Jay



Summary

Background In hot weather, electric fans can potentially provide effective cooling for people, with lower greenhouse gas emissions and cost than air conditioning. However, international public health organisations regularly discourage fan use in temperatures higher than 35°C, despite little evidence. We aimed to determine humidity-dependent temperature thresholds at which electric fans would become detrimental in different age groups.

Methods We used biophysical modelling to determine the upper humidity-dependent temperature thresholds at which fan use would become detrimental (ie, worsen heat stress) for healthy young adults (aged 18–40 years), healthy older adults (aged ≥65 years), and older adults taking anticholinergic medication. We also obtained hourly environmental data for the period Jan 1, 2007, to Dec 31, 2019, for 108 populous cities to determine the number of days fan use would be effective for cooling, standardised to a 31-day hot weather month. We established simplified temperature thresholds for future fan use recommendations on the basis of temperatures below which fan use would never have been detrimental between Jan 1, 2007, and Dec 31, 2019, across all prevailing levels of ambient humidity.

Findings According to our model, fan use would have been beneficial on 30·0 (96·6%) of 31 hot weather days for healthy young adults and 29·4 (94·9%) of 31 hot weather days for both older adults and older adults taking anticholinergic medication between Jan 1, 2007, and Dec 31, 2019. Adherence to the current WHO recommendation of fan use below temperatures of 35°C only, fan use would have been recommended on 27·2 days (87·7%) of 31 hot weather days. According to our simplified thresholds for fan use (at temperatures <39·0°C for healthy young adults, <38·0°C for healthy older adults, and <37·0°C for older adults taking anticholinergic medication), fan use would have been recommended on 29·6 (95·5%) of 31 hot weather days in healthy young adults, 29·4 (94·8%) days in healthy older adults, and 28·8 (93·0%) days in older adults taking anticholinergic medication between Jan 1, 2007, and Dec 31, 2019.

Interpretation Electric fan use, particularly for healthy young adults, would not have worsened heat stress on the majority of study days between 2007 and 2019. Our newly proposed thresholds for fan use provide simple guidelines that improve future heatwave fan use recommendations.

Funding None.

Copyright © 2021 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY-NC-ND 4.0 license.

Introduction

Air conditioning has been found to be the most effective method for reducing mortality¹ and morbidity,² and improving thermal comfort during heatwaves. Personal air conditioning use (eg, mobile and residential) accounts for 56% of all cooling technology units sold globally.³ However, air conditioning use substantially contributes to global greenhouse gas emissions and directly contributes to the urban heat island effect.⁴ Older air conditioning units use chlorofluorocarbons as refrigerant gases, which deplete the ozone layer, whereas newer units use hydrofluorocarbons, which can be thousands of times more potent greenhouse gases than carbon dioxide (CO₂), and at present, are the fastest growing greenhouse gases emitted globally.¹ Air conditioning use is responsible for 65% of global hydrofluorocarbon emissions and it is predicted that the increase in global hydrofluorocarbon release will result in a 0·25–0·50°C increase in the mean

surface temperature of Earth.⁵ At present, air conditioning use (in combination with refrigeration) accounts for 7–10% of annual CO₂ emissions due to its high energy demand.³ In the eastern regions of the USA alone, it is predicted that increases in greenhouse gas emissions due to air conditioning use will increase pollution-related mortality by 5–9% (~13,500 deaths) by 2050, resulting in an additional US\$126 billion in health-care costs.⁵ Globally, air conditioning use is increasing rapidly, largely driven by improvements in living standards in many low-income and middle-income countries.⁶ The provision of cooling solutions in low-income and middle-income countries has been directly linked to achieving the UN Sustainable Development Goals, since cooling reinforces targets associated with food security, health, education, and social inequality, among other goals,³ and therefore cannot be forgone altogether. However, it is predicted that 700 million new air conditioning units will be in use

Lancet Planet Health 2021;
S: e368–77

Thermal Ergonomics Laboratory (N B Morris PhD, G K Chaseling PhD, T English PhD, F Gruss MSc, M F B Maideen MPhil, Prof O Jay PhD), Sydney School of Public Health (Prof A Capon PhD, Prof O Jay), Faculty of Medicine and Health, and Charles Perkins Centre (T English, Prof O Jay), The University of Sydney, Sydney, NSW, Australia; Department of Nutrition, Exercise and Sports, University of Copenhagen, Copenhagen, Denmark (N B Morris); Department of Pharmacology and Physiology, University of Montreal, Montreal, QC, Canada (G K Chaseling); Monash Sustainable Development Institute, Monash University, Melbourne, VIC, Australia (Prof A Capon)

Correspondence to: Prof Ollie Jay, Thermal Ergonomics Laboratory, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW 2006, Australia. ollie.jay@sydney.edu.au

Research in context

Evidence before this study

Air conditioning substantially contributes to greenhouse gas emissions directly through leakage of refrigerant gases into the atmosphere and indirectly due to the high electrical demands. Comparatively, electric fan use requires no refrigerant gases and requires 30 to 50 times less energy to operate than air conditioning. Despite these benefits, many public health organisations discourage electric fan use in ambient temperatures of around 35°C and higher. We searched PubMed, the Cochrane Library, and PROSPERO for systematic reviews from database inception to May 5, 2020, pertaining to heatwave cooling recommendations. For systematic reviews older than 5 years, we used their stated search terms to identify novel recent papers. Our search identified two systematic reviews on cooling interventions during heatwaves and eight publications on fan use. A 2012 Cochrane review concluded that there was no evidence in the literature to support or refute the use of electric fans in a heatwave. Studies done in 2015 and 2016 found that fan use was physiologically beneficial at 42°C in humid conditions in young adults, but not in older adults (aged 60–80 years; due to a reduced sweating response), whereas a 2019 study in young adults demonstrated fan use to be effective for reducing physiological heat strain at 40°C with 50% relative humidity, but accelerated body heating at 47°C with 10% relative humidity.

Added value of this study

We developed biophysical models on the basis of fundamental principles of heat exchange between humans and the environment, with physiological parameters defined by human thermoregulatory laboratory data, to determine the

humidity-dependent temperature thresholds at which fans would become detrimental. On the basis of weather data for the period Jan 1, 2007, to Dec 31, 2019, we found that contrary to many public health recommendations, electric fan use could have been universally recommended for young healthy adults during peak heatwave conditions in all of the populous cities in Bangladesh, China, Japan, Philippines, Indonesia, Canada, eastern regions of the USA, all of South America and Oceania, and most of Europe (excluding some Mediterranean cities). Fan use alone should not have been routinely recommended during hot weather in northern India, Pakistan, the Middle East, and the southwestern regions of the USA.

Implications of all the available evidence

Compared with air conditioning, electric fan use is a more sustainable cooling modality, and more widely accessible in low-income and middle-income countries. The effectiveness of fan use is dependent on temperature and relative humidity. Our findings indicate that for younger adults, fan use during peak heatwave conditions can be recommended most of the time in most regions of the world (with the exception of extremely hot and arid regions). In the 12 countries estimated to have the greatest potential for growth in air conditioner use by the end of the 21st century (combined population of around 4.25 billion individuals), for young healthy adults, fan use could have been recommended on 30.6 (98.6%) of 31 hot weather days in the study period. However, for healthy older adults and particularly those taking anticholinergic medications that impair sweating, fan use would occasionally be detrimental and worsen heat stress; therefore alternative cooling strategies are needed in some regions.

worldwide by 2030;⁷ thus more sustainable strategies for cooling people are urgently needed.

Moving air across the skin with devices such as electric fans offers an individual-level cooling strategy that bypasses the issues associated with refrigerant gases and decreases electricity requirements by 30 times.⁸ The lower electricity requirements and cost help to mitigate additional negative compounding health factors such as socioeconomic inequality, poor access to air conditioning, and overwhelming power grids (thereby hindering emergency services) during power outages.⁹ Despite these advantages, many leading national and international public health authorities such as the Environmental Protection Agency,¹⁰ US Centers for Disease Control and Prevention,¹¹ the UK National Health Service,¹² and WHO¹³ currently advise that electric fans provide no cooling benefits or can even accelerate body heating in ambient temperatures of 35°C and higher, irrespective of relative humidity levels. However, none of these recommendations are based on any experimental data, and a 2012 Cochrane review¹⁴ concluded that no evidence exists to support or refute the effectiveness of fans in a heatwave, highlighting the need for more research in this area.^{14,15}

The probable origin of the existing 35°C threshold for fan use is that once ambient temperature exceeds skin temperature (around 35°C), fan use will increase the rate of convective heat gain to the body from the surrounding environment,¹⁰ which can markedly increase the rate of sweat evaporation.¹⁶ Accordingly, whether fan use is beneficial for cooling people at ambient temperatures higher than 35°C is dependent on ambient humidity and their ability to sweat. In laboratory-based physiological studies, we found that in young adults without sweating impairment, fan use provided effective cooling, confirmed by blunted heat-related rises in core temperature and heart rate, at temperatures of 40°C¹⁷ and 42°C¹⁸ with around 50% relative humidity. However, at temperatures of 47°C with low relative humidity (around 10%), fan use accelerated the development of hyperthermia because sweat readily evaporates in these conditions even without a fan, but convective heat gain continues.¹⁷ The benefit of fan use is reduced, and might even be detrimental, at 42°C with more than 50% relative humidity in older adults (aged >65 years), due to roughly 25% reductions in sweat losses relative to young adults.^{19,20} Furthermore, the ability to sweat in individuals taking anticholinergic medication,

which, for example, are prescribed by general practices to around 12% of geriatric patients (aged 65–101 years) in Slovenia,²¹ is reduced by a further 25% when compared with young adults.²² Collectively, these physiological studies demonstrated that fan use can be recommended at higher temperature thresholds than 35°C for some populations; however, humidity levels are crucial for determining fan use temperature thresholds, and fan use recommendations must be altered for people with physiologically or pharmacologically impaired sweating.

To recommend fan use more widely would be clearly enticing, considering the environmental benefits, and to increase the adaptive capacity of individuals who cannot afford or gain access to air conditioning. However, accurate, evidence-based guidelines are needed to ensure fan use is not recommended in conditions that would accelerate heat stress.¹⁷ Biophysical modelling can be used to develop humidity-dependent temperature thresholds for beneficial fan use, whereby changes in dry and evaporative heat transfer with different levels of sweating can be calculated and the combinations of ambient temperature and humidity at which fan use accelerates net heat transfer toward, as opposed to away from, the body can be determined.

We developed three biophysical models to determine the environmental conditions in which fan use would become detrimental for different age groups. Additionally, we contextualised these environmental thresholds to real-world conditions for 108 of the most populous cities in the world with a particular focus on 59 cities from the 12 countries identified to have the greatest potential for growth in air conditioning use by the end of the 21st century.⁶

Methods

Biophysical models

We used biophysical models to generate three upper environmental condition thresholds (all combinations of temperature and relative humidity), above which whole-body fan use would become detrimental (ie, worsen heat stress) for healthy young adults (aged 18–40 years), healthy older adults (aged ≥65 years), and older adults taking anticholinergic medication. These age groups were selected because the ability to sweat is reduced by 25% in older adults compared with young healthy adults,¹⁹ and is decreased by a further 25% in individuals on anticholinergic medication.²³ The three threshold curves were built using standard, well-validated, partitioned calorimetry equations frequently used in military, thermal comfort, and athletic applications,¹⁶ which calculate the net heat transfer between a person and their environment via all available physical pathways (ie, conduction, convection, radiation, and evaporation). Accordingly, the net heat transfer of a person, lightly clothed and seated at rest (or lying on a bed for the night-time analysis), either in front of a standard pedestal fan (air speed 3.5 m per sec) or without a fan (air speed 0.2 m per sec) were

compared across a range of temperature and relative humidity condition combinations. The temperatures and corresponding relative humidity values at which net heat loss from the body to the surrounding environment was greater without fan use than with a fan were defined as the upper environmental threshold for electric fan use. Subsequently, using these environmental threshold values, we defined a humidity-dependent fourth order polynomial model using GraphPad Prism (version 8.0) to create threshold curves for young healthy adults, older adults, and older adults on anticholinergic medication for both day and night applications. Full details of all equations and assumptions used to produce the models are in the appendix (pp 3–10).

See Online for appendix.

Global weather analysis

To contextualise the conditions in which fan use would be beneficial or detrimental, we obtained hourly environmental data from the airport weather stations of 108 global cities for the period Jan 1, 2007, to Dec 31, 2019. A complete list of cities with individualised and regional results are included in the appendix (pp 16–47). We selected the five cities with the largest populations in specific countries and on the basis of geographical locations across all six habitable continents (North America, Europe, Asia, South America, Oceania, and Africa) to represent a wide range of hot weather conditions. We also selected 59 of the 108 cities to focus on the most populous cities in each of the 12 countries that have previously been estimated to have the greatest potential for growth in air conditioning use by the end of the 21st century: India, China, Indonesia, Nigeria, Pakistan, Bangladesh, Brazil, Philippines, the USA, Vietnam, Thailand, and Mexico.⁶ We selected the time period of Jan 1, 2007, to Dec 31, 2019, because this included eight of the ten warmest years on record globally.²⁴ We purchased all climatic data from CustomWeather. For countries geographically located north of the Tropic of Cancer (23.44° North) or south of the Tropic of Capricorn (23.44° South), we only analysed weather data for the five warmest months of the year (May to September in the northern hemisphere; November to March in the southern hemisphere). For countries located within the tropics, we analysed weather data for the whole year. We also separated and analysed data for daytime hours (sunrise to sunset) and night-time hours (2100h to 0600h) separately.

For more on CustomWeather see <https://customweather.com>

The outcomes of interest were: peak weather conditions (highest hourly temperature and concomitant relative humidity value), 95th percentile weather conditions, and the number of days and nights exceeding the fan use thresholds defined by each model (ie, the number of days or nights that fan use would worsen heat stress for young healthy adults, older adults, and older adults taking anticholinergic medication). Additionally, since regular fluid replacement does not occur at night during sleep and public health organisations have previously warned against the use of fans at night because of concerns

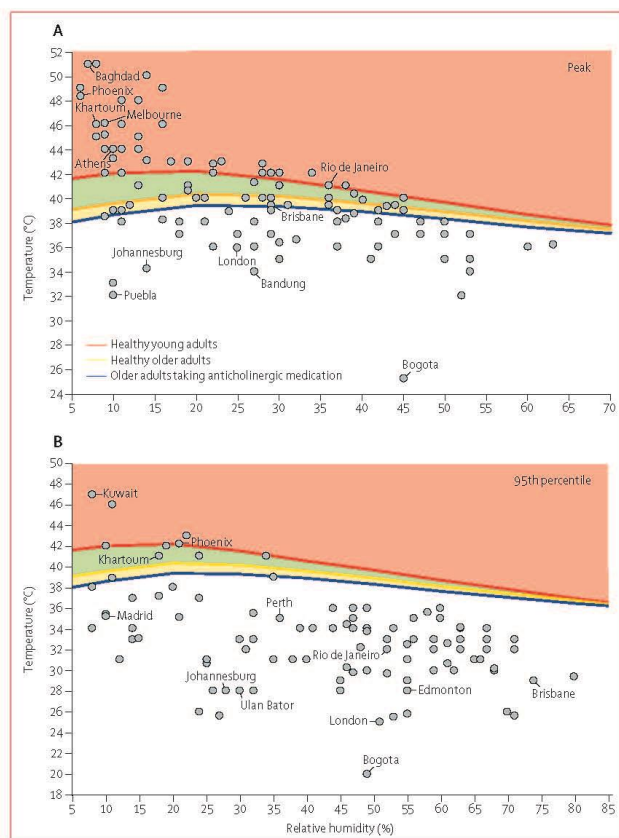


Figure 1: Daytime humidity-dependent temperature threshold curves with peak and 95th percentile hot weather conditions recorded in 108 cities (Jan 1, 2007, to Dec 31, 2019) (A) Highest single 1 h daytime ambient temperature with parallel relative humidity. (B) 95th percentile daytime hot weather conditions. Daytime humidity-dependent temperature threshold curves show the temperatures above which electric fan use becomes detrimental (ie, worsens heat stress). Yellow shading represents conditions in which fan use would worsen heat stress for older adults taking anticholinergic medication only. Green shading represents conditions in which fan use would worsen heat stress for older adults and older adults taking anticholinergic medication, but not healthy young adults. Red shading represents conditions in which fan use would worsen heat stress for all age groups.

about excessive dehydration from accelerated sweat evaporation,¹¹ in the night-time analysis, we estimated sweat losses with fan use, on the basis of the amount of sweat loss required to maintain heat balance. No sweat nights were defined as nights when fan use would eliminate the need to sweat, high sweat nights were defined as nights when sweat rates would exceed 180 mL per h (ie, the sweat rate required to induce more than 2% of total body-mass dehydration for a person weighing 70 kg without fluid replacement over 8 h), and low sweat nights were defined as nights that fell between the

two previous zones (appendix pp 37–47). To account for differences in analysed days between geographical areas, days exceeding the fan use thresholds (daytime or night-time) or days exceeding night-time sweating thresholds were expressed as days per hot-month, with a maximum value of 31 days (ie, a 31-day hot weather month). The effectiveness of fan use on days that temperatures were 35.5°C or higher (higher than the current WHO-recommended threshold of 35°C for fan use) and proposed simplified temperature thresholds based on the present model were analysed separately, to characterise how many days fan use would have been unnecessarily discouraged by WHO recommendations.

Role of the funding source

There was no funding source for this study.

Results

The complete equations for the fourth order polynomial models for the humidity-dependent temperature thresholds for safe fan use and a full summary of the data for all cities analysed, stratified by continent and peak air conditioning use countries, are included in the appendix (pp 9, 11, 15–47). Peak and 95th percentile daytime weather conditions for all 108 cities were plotted alongside each threshold curve (figure 1). Mean peak temperature was 40.0°C (SD 4.2) with 27% relative humidity (SD 15) and mean 95th percentile daytime temperature was 33.0°C (4.4) with 44% relative humidity (19). During peak conditions, fan use would have been beneficial (ie, provided a cooling effect) in 75 (69.4%) of 108 cities for young healthy adults, 60 (56%) for healthy older adults, and 44 (40.7%) for older adults taking anticholinergic medication. In the 95th percentile conditions, fan use would have been beneficial in 104 (96%) of 108 cities for young healthy adults, 99 (91.7%) for healthy older adults, and 98 (90.7%) for older adults taking anticholinergic medication. Of the 59 cities (in 12 countries) with the greatest potential for growth in air conditioning use by the end of the century, during peak conditions, fan use would have been beneficial in 40 (67.8%) cities for young healthy adults, 30 (50.8%) for healthy older adults, and 19 (32.2%) for older adults taking anticholinergic medication; for the 95th percentile conditions, fan use would have been beneficial in 58 (98.3%) cities for young healthy adults, 54 (91.5%) for healthy older adults, and 53 (89.8%) for older adults taking anticholinergic medication. The lowest temperature below which fan use would never have been detrimental across all levels of relative humidity, for each city and by continents is in the appendix (pp 15–33). Globally, the temperatures below which fan use would always be beneficial irrespective of humidity levels present were 39.0°C for young healthy adults, 38.0°C for healthy older adults, and 37.0°C for older adults taking anticholinergic medication.

The number of days, expressed as a 31-day monthly average, falling below each humidity-dependent

	Global	North America	Europe	Asia	South America	Oceania	Africa	12-AC
Days per 31-day hot weather month fan use would have a cooling effect according to fourth order polynomial model, n (%)								
Healthy young adults	30.0 (96.6%)	30.5 (98.5%)	31.0 (100.0%)	29.0 (93.6%)	31.0 (100.0%)	30.9 (99.6%)	30.7 (98.9%)	30.6 (98.6%)
Healthy older adults	29.4 (94.9%)	30.0 (96.6%)	30.9 (99.8%)	28.2 (91.1%)	31.0 (100.0%)	30.6 (98.7%)	29.9 (96.5%)	30.1 (97.0%)
Older adults taking anticholinergic medication	29.4 (94.9%)	29.7 (95.7%)	30.9 (99.7%)	28.4 (91.7%)	31.0 (100.0%)	30.4 (98.2%)	29.5 (95.3%)	29.7 (95.9%)
Days per 31-day hot weather month fan use would have a cooling effect according to WHO recommendations, n (%)								
Overall	27.2 (87.7%)	27.7 (89.4)	30.2 (97.4%)	25.3 (81.5%)	30.9 (99.6%)	29.2 (94.1%)	26.8 (86.5%)	27.0 (87.1%)
Days per per 31-day hot weather month fan use would have a cooling effect according to novel simplified thresholds, n (%)								
Healthy young adults	29.6 (95.5%)	29.8 (96.0%)	30.9 (99.8%)	28.7 (92.7%)	31.0 (100.0%)	30.6 (98.6%)	29.8 (96.0%)	29.9 (96.6%)
Healthy older adults	29.4 (94.8%)	29.4 (94.9%)	30.9 (99.6%)	28.5 (91.8%)	31.0 (100.0%)	30.3 (97.9%)	29.5 (95.1%)	29.6 (95.5%)
Older adults taking anticholinergic medication	28.8 (93.0%)	28.9 (93.1%)	30.8 (99.2%)	27.7 (89.3%)	31.0 (100.0%)	30.0 (96.9%)	28.8 (92.9%)	28.9 (93.3%)
Additional days per 31-day hot weather month fan use can be recommended according to our simplified thresholds compared with WHO threshold, n (% improvement)								
Healthy young adults	2.4 (7.8%)	2.1 (6.6%)	0.7 (2.4%)	3.4 (11.2%)	0.1 (0.4%)	1.4 (4.5%)	3.0 (9.5%)	2.9 (9.5%)
Healthy older adults	2.2 (7.1%)	1.7 (5.5%)	0.7 (2.2%)	3.2 (10.3%)	0.1 (0.4%)	1.1 (3.8%)	2.7 (8.6%)	2.6 (8.4%)
Older adults taking anticholinergic medication	1.6 (5.3%)	1.2 (3.7%)	0.6 (1.8%)	2.4 (7.8%)	0.1 (0.4%)	0.8 (2.8%)	2.0 (6.4%)	1.9 (6.2%)

The mean number of days on which fan use would have been beneficial was standardised to a monthly average of 31 days to account for differences in number of days analysed due to geographical location. SDs are shown in the appendix (pp 15–36). 12-AC=12 countries with the greatest potential for growth in air conditioning use by the end of the century.⁶

Table 1: Mean number of hot weather days per month fan use would have been beneficial by geographical location

temperature threshold for fan use, globally, by continent, and for the 12 peak air conditioning use countries are reported in table 1. Globally, according to our model, fan use would have been beneficial on 30 (96.6%) of 31 hot weather days between Jan 1, 2007, and Dec 31, 2019, for young healthy adults and 29.4 (94.8%) hot weather days for healthy older adults and older adults taking anticholinergic medication, whereas of the 12 countries with the greatest potential for growth in air conditioning use by the end of the 21st century, fan use would have been beneficial for 30.6 (98.6%) hot weather days for young healthy adults, 30.1 (97.0%) hot weather days for healthy older adults, and 29.7 (95.9%) hot weather days for older adults taking anticholinergic medication. These values contrast with the previous WHO recommendations, which would have recommended fan use on 27.2 (87.7%) of 31 hot weather days between Jan 1, 2007, and Dec 31, 2019, for all three groups. If the proposed simplified thresholds for fan use (ie, 39.0°C for young healthy adults, 38.0°C for healthy older adults, and 37.0°C for older adults taking anticholinergic medication) had been adopted between Jan 1, 2007, and Dec 31, 2019, fan use would have been recommended on 29.6 (95.5%) of 31 hot weather days for young healthy adults, 29.4 (94.8%) hot weather days for healthy older adults, and 28.8 (93.0%) hot weather days for older adults taking anticholinergic medication. A historical daytime analysis

for younger and older adults is summarised in a global map (figure 2).

During the night, the mean peak temperature was 34.1°C (SD 4.1) with 41% (SD 21) relative humidity and the mean 95th percentile night-time temperature was 27.4°C (4.0) with 64% (22) relative humidity (figure 3). During peak conditions, fan use would have a cooling effect in 97 (89.8%) of 108 cities for young healthy adults, 93 (86.1%) cities for healthy older adults, and 87 (80.6%) cities for older adults taking anticholinergic medication (figure 3A). In the 95th percentile conditions, fan use would have a cooling effects in all 108 (100%) cities for all three age groups (figure 3B). Of the 59 cities (across 12 countries) with the greatest potential for growth in air conditioning use by the end of the 21st century, during peak conditions, fan use would have a cooling effect in 48 (81.4%) cities for young healthy adults, 44 (74.6%) for healthy older adults, and 38 (64.4%) for older adults taking anticholinergic medication; for the 95th percentile conditions, fan use would have had a cooling effect in all 59 (100%) cities for all three analysis groups.

The number of nights, expressed as a monthly average, exceeding each humidity-dependent temperature threshold for fan use, globally, by continent, and for the 12 countries with the greatest potential for growth in air conditioning use by the end of the 21st century are shown in table 2. Globally, standardised to a 31-day hot weather

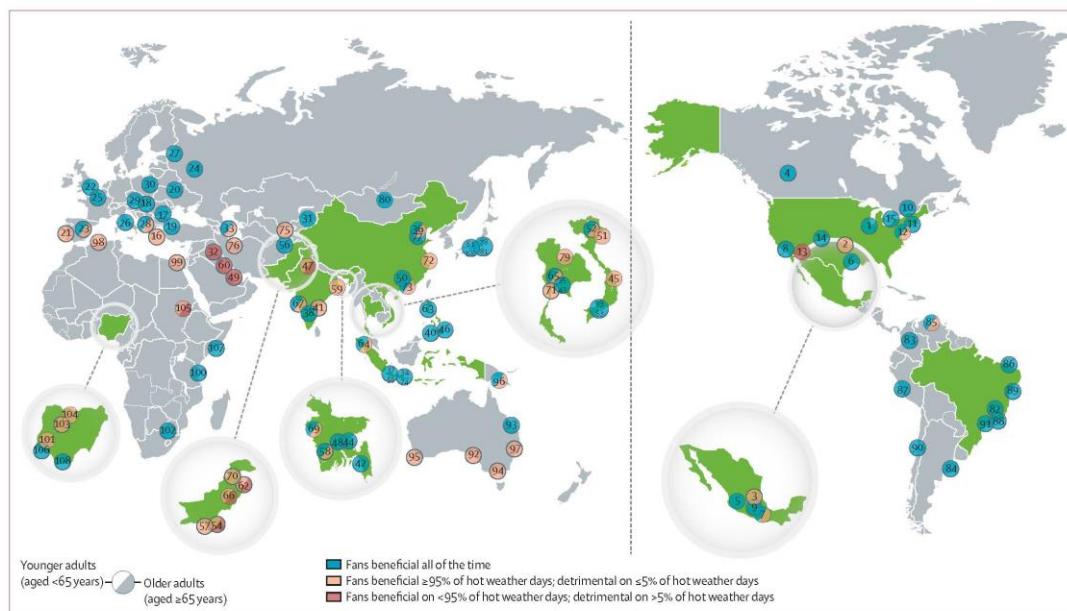


Figure 2: Fan use recommendations according to proposed biophysically modelled humidity-dependent temperature threshold curves for healthy younger and healthy older adults based on the peak and 95th percentile environmental conditions recorded between Jan 1, 2007, and Dec 31, 2019. Countries highlighted in green represent those identified as the 12 countries with the greatest potential for growth in air conditioning use by the end of the 21st century.⁶ A list of cities corresponding to the numbers in the figure is included in the appendix (pp 15–36).

month, fan use would have been beneficial on 30·9 (99·8%) nights for healthy young adults, 30·9 (99·5%) nights for healthy older adults, and 30·7 (99·1%) nights for older adults taking anticholinergic medication. Collectively, fan use would have elicited either no sweating or a sweating rate lower than the sweat rate threshold for dehydration on 0·7 (2·3%) nights.

Specifically, for the 12 countries with the greatest potential for air conditioning use by the end of the 21st century, fan use would have been beneficial for 31·0 (99·9%) nights for healthy young adults, 30·9 (99·8%) nights for healthy older adults, and 30·9 (99·5%) nights for older adults taking anticholinergic medication. For the 59 cities analysed in these countries, fan use would have elicited either no sweating or a sweating rate lower than the sweat rate threshold for dehydration on 0·4 (1·4%) nights (appendix pp 37–47).

Discussion

In this study, we used biophysical modelling to generate humidity-dependent temperature curves describing the conditions at which electric fans become detrimental (ie, worsen heat stress) for young healthy adults, healthy older adults, and older adults taking anticholinergic medication. These thresholds were compared with hourly hot weather

data for 108 populous cities between Jan 1, 2007, and Dec 31, 2019 (appendix pp 15–47). Based on our analysis, fan use during the day would have been beneficial (ie, higher net heat loss from the body to the surrounding environment than with no fan use) on every day of the analysis period in 69% of the 108 cities for young adults, 56% of the cities for healthy older adults, and 41% of the cities for older adults taking anticholinergic medication analysed during the day, and beneficial during the night in 90% of 108 cities for young adults, 86% of the cities for healthy older adults, and 81% of the cities for older adults taking anticholinergic medication. Our findings broadly illustrate how the effectiveness of fan use varies depending on the prevailing weather conditions in each geographical area and the thermoregulatory capacity of the individual; however, there are many locations on Earth where fan use could be safely recommended as an alternative to air conditioning all of the time despite air temperature exceeding the currently recommended threshold of 35°C. For many additional locations, climatic conditions wherein fan use would have been detrimental were exceptions to the general pattern and could be a recommended alternative for the majority of time, with the exception of the warmest 1–2 h of the day during the warmest 1–3 days recorded during the 13-year time period assessed.

At present, air conditioning use is responsible for 65% of global hydrofluorocarbon emissions and, in combination with refrigeration, 7–10% of global CO₂ emissions.³ The greenhouse gas effect of hydrofluorocarbons is 1–3 orders of magnitude greater than CO₂, with the change in mean Earth surface temperature projected to increase by 0.25–0.5°C by the end of the 21st century due to hydrofluorocarbon emissions alone.³ Projections for air conditioning use only slightly differ between moderate (representative concentration pathway 4.5) and high (representative concentration pathway 8.5) greenhouse gas emission models, highlighting that domestic air conditioning use will continue to be a substantial contributor to greenhouse gas emissions, regardless of the effectiveness of other methods to reduce emissions.⁶ Based on 2015 UN world demographic data,²⁴ 6.78 billion (92%) of the 7.38 billion global population were aged younger than 65 years and therefore represented by the young healthy adults model in this study. As a crude estimate, if all of these young people were to switch from air conditioning to fan use for their cooling needs, when fan use would be beneficial, this would theoretically yield a 59% reduction in global hydrofluorocarbon emissions and around a 9% reduction in global CO₂ emissions. Although reductions to this degree are unrealistic, these values are indicative of the large potential reductions in global greenhouse gas emissions that could be achieved by transitioning from cooling air with air conditioning to moving air with devices such as electric fans.

From our global hot weather analysis, electric fan use would have provided cooling benefits for 96.6% of all hot weather days in the study period analysed for young adults, and 94.9% of days for healthy older adults and older adults taking anticholinergic medication. These findings differ substantially from the current recommendations of most international health authorities and mainstream media outlets during peak heatwave conditions. For example, in 2018, the UK media warned against the use of fans above temperatures of 35°C.²⁵ Conversely, our hourly historical weather analysis of London revealed the peak recorded temperature since 2007 was 35.9°C with 25% relative humidity, under which our models demonstrate that fan use can be universally recommended for all individuals. The highest temperature recorded for the UK reported in Cambridge in 2019 was 38.7°C with 31% relative humidity. According to our humidity-dependent temperature threshold curves, fan use would have been beneficial under these conditions for both young and healthy older adults, but not older adults taking anticholinergic medication.

According to our historical day-time analysis, fan use could have been universally recommended to both young and older adults across large areas of northern Europe, northeastern regions of the USA, Canada, all of South America, and much of southeast Asia. In contrast, fan use could have generally been considered inadvisable in

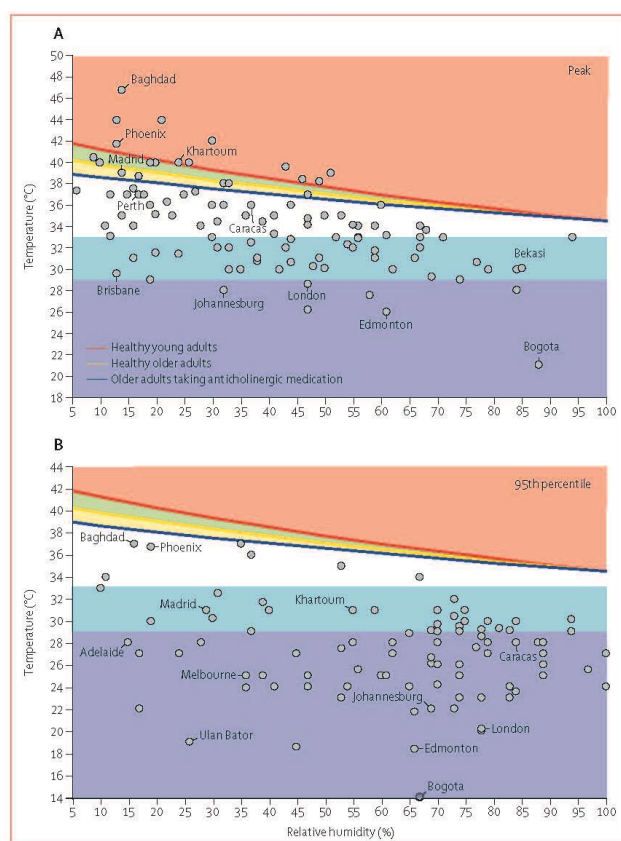


Figure 3: Night-time humidity-dependent temperature threshold curves with peak and 95th percentile hot weather conditions recorded in 108 cities (Jan 1, 2007, to Dec 31, 2019). (A) Highest single 1 h night-time ambient temperature. (B) 95th percentile night-time hot weather conditions. White areas denote conditions that elicit heavy sweating (>2% of body weight loss from sweating in 8 h) with fan use, light blue areas denote conditions that elicit light sweating (<2% of body weight loss in 8 h) with fan use, and dark blue areas denote conditions that elicit no sweating with fan use. Yellow shading represents conditions in which fan use would worsen heat stress for older adults taking anticholinergic medications only. Green shading represents conditions in which fan use would worsen heat stress for healthy older adults and older adults taking anticholinergic medications, but not healthy young adults. Red shading represents conditions in which fan use would worsen heat stress for all age groups.

exceptionally arid areas such as the Middle East and southwestern regions of the USA, and on the hottest heatwave days in very humid (ie, not just humid but very humid) regions such as northern India and Pakistan.

Geographical areas of particular interest are the 12 countries identified as having the greatest potential for growth in air conditioning use by the end of the 21st century, where it is estimated that residential electrical consumption will increase by 83% based on weather conditions, population, and current air

	Global	North America	Europe	Asia	South America	Oceania	Africa	12-AC
Nights per month fan use would have had a cooling effect								
Healthy young adults	30.9 (99.8%)	31.0 (100.0%)	31.0 (100.0%)	30.9 (99.6%)	31.0 (100.0%)	31.0 (100.0%)	31.0 (100.0%)	31.0 (99.9%)
Healthy older adults	30.9 (99.5%)	30.9 (99.7%)	31.0 (100.0%)	30.7 (99.1%)	31.0 (100.0%)	31.0 (100.0%)	30.9 (99.8%)	30.9 (99.8%)
Older adults taking anticholinergic medication	30.7 (99.1%)	30.8 (99.4%)	31.0 (100.0%)	30.5 (98.4%)	31.0 (100.0%)	31.0 (100.0%)	30.8 (99.4%)	30.9 (99.5%)
Nights with fan use								
No sweating	27.9 (89.9%)	28.1 (90.7%)	30.1 (97.2%)	26.1 (84.2%)	30.9 (99.6%)	30.2 (97.4%)	28.7 (92.7%)	27.6 (88.9%)
Low sweating	2.4 (7.8%)	2.2 (7.2%)	0.8 (2.5%)	3.8 (12.2%)	0.1 (0.4%)	0.8 (2.4%)	1.6 (5.2%)	3.0 (9.7%)
High sweating	0.7 (2.3%)	0.7 (2.2%)	0.1 (0.2%)	1.1 (3.6%)	0.0 (0.0%)	0.0 (0.1%)	0.7 (2.1%)	0.4 (1.4%)

Data are n (%). The mean number of nights on which fan use would have been beneficial was standardised to a monthly average of 31 days to account for differences in number of days analysed due to geographical location. High sweating was defined as >2% bodyweight loss from sweating in 8 h and low sweating was defined as ≤2% bodyweight loss from sweating in 8 h. SDs are shown in the appendix (pp 37–47). 12-AC=the 12 countries with the greatest potential for growth in air conditioning use by the end of the 21st century.⁶

Table 2: Mean number of hot weather nights per month on which fan use would have had a cooling effect according to our model, by geographical region, and predicted overnight sweat losses

conditioning use trends, collectively comprising more than half of the global population (4.25 billion people).⁶ Most of these countries are tropical and, as such, heat stress conditions are predominantly characterised as hot and humid; the conditions wherein clinical trials have demonstrated fan use to be effective for cooling in young healthy adults.¹⁷ At present, many of these countries do not have the infrastructure to support the electricity required to operate the increasing number of air conditioning units, and therefore are at high risk of power disruptions that disturb economic output²⁶ and threaten the capacity of health-care systems as a result of further surges in heat-related mortality and morbidity.⁹

One of the most common public health concerns regarding electric fan use during heatwaves is the potential acceleration of dehydration.¹¹ Sweat loss has been experimentally confirmed to be greater with fan use at ambient temperatures exceeding 35°C.^{17,18} Hydration requirements seem to be sufficiently met by allowing people to drink to prevent thirst in young healthy adults;²⁷ however, this finding has not yet been confirmed during extended heatwave conditions in older adults or in those taking medication who might demonstrate blunted thirst. Additionally, during sleep at night, opportunities for water ingestion are reduced, and therefore dehydration is more likely to occur with increased sweat rates. Supporting this notion, hydration data from European workers in five different sectors showed that with the exception of agricultural workers, people often arrived at work on summer mornings objectively dehydrated according to urine specific gravity measurements.²⁸ From a hydration-maintenance perspective, fan use at night, as opposed to during the day, is particularly desirable in many cases: according to our data, fan use would negate the need to sweat at all (due to increases in non-evaporative convective heat loss) on 89.9% of nights, while keeping sweat losses below 2% of body weight

across an 8 h period, which is approximately the tolerable threshold before dehydration-related exacerbations of physiological strain occur;²⁹ on a total of 97.7% of nights (ie, the sum of no sweating and low sweating nights). For the remaining 2.3% of nights, electric fan use would not be recommended and people would be encouraged to seek alternative forms of cooling, such as air conditioning.

For people taking anticholinergic medication or living in locations where fan use was deemed to be detrimental on some hot weather days, the use of air conditioning would be necessary, potentially threatening the wellbeing of people with low income living in these areas. A 2019 study has shown that in healthy young adults, self-dousing with water reduces thermal and cardiovascular strain in both hot and dry (47°C and 10% relative humidity) conditions and in hot and humid (40°C and 50% relative humidity) simulated heatwave conditions, while reducing natural sweat losses,³⁰ providing effective potential alternatives to fan use during waking hours when air temperatures peak. Additionally, wearing a water-saturated shirt has been shown to reduce thermal and cardiovascular strain and dehydration in healthy older individuals (aged 62–74 years) in conditions of 42°C with 34% relative humidity,³¹ and could potentially be beneficial for offsetting dehydration in extreme night-time temperatures.

Although the threshold curves were constructed using standard partitioned calorimetric calculations¹⁶ that have been used extensively and are well validated, modelled data should be interpreted with caution in the absence of accompanying clinical data. The findings from the model for young healthy adults was consistent with the clinical data available;¹⁷ accordingly the recommendation for young healthy adults to use fans seems to be empirically supported, since at peak temperatures there was not a single day in which air temperature surpassed 40°C in 66 (61%) of the 108 global cities analysed and 34 (58%) of the 59 cities with the highest air conditioning use. More clinical studies are required to verify the findings for

older adults and those on prescription medication (especially anticholinergics); however, the physiological parameters (ie, sweat rates) in our models that were adjusted for these groups were conservative, and as such are likely to underestimate the efficacy of fan use in these groups. Additionally, the conditions in our model were fixed for a person seated at rest with a set clothing ensemble. Differences in effectiveness of fans will vary based on clothing and activity level and, therefore, these findings should not be extrapolated to individuals doing physical activity. To date, all clinical studies to date have been done over a short duration in peak temperature conditions simulated in climate chambers. Verification of these findings in field-based clinical trials during full length heatwaves is required.

All weather data in this study were collected from airport weather stations, and thus differences between inner city temperatures and indoor temperatures will exist. An Italian study found that the mean peak temperature of three different cities was 1–1°C higher in the city compared with the airport; however, humidity levels (expressed as dew point temperature) were 2–7°C higher at the airport than the city sites.³² Temperature differences will be airport specific: in a study done in New York, temperatures reported at John F Kennedy International Airport (which receives a sea breeze) were around 8°C lower than the warmest inner-city weather station, whereas at LaGuardia Airport (which has no sea breeze) temperatures were under-reported by around 5°C.³³ Furthermore, indoor temperatures will vary considerably based on the materials used to construct buildings. For example, painting outdoor building surfaces with highly reflective paint can reduce indoor temperatures by 6°C.³⁴ Conversely, two studies that included indoor air temperature from low-income housing found that peak indoor temperatures were lower than peak outdoor temperatures by 1–3°C during the day, but were higher than outdoor temperatures by around 7°C at night.^{33,35} The inclusion of new simplified temperature thresholds for fan use in this study could help to counteract these issues by informing the public to use fans below these thresholds according to indoor thermometers. It is well established that mean global temperatures,³⁶ and specific humidity values to a lesser degree,³⁷ will continue to rise during this century and, therefore, the effectiveness of fan use is likely to decline. Future research is therefore needed to establish the effectiveness of fans in urban, indoor, and future climatic scenarios.

In conclusion, the effectiveness of fan use for cooling young healthy adults is evident, since peak temperatures between 2007 and 2019, a time period that included eight of the ten hottest years on record, did not exceed the upper threshold for effective fan use for even 1 h in 69% of the cities during the day and 90% of the cities at night. Fan use would have collectively provided effective cooling for young adults on 97% of all days analysed, and more than 98% of all nights (while avoiding critical

dehydration). Although peak temperatures exceeded the upper threshold for effective fan use for at least 1 day in 59% of the cities for older adults taking medication that impair sweating, fan use in this population would have been effective on 95% of hot weather days in the study period and more than 98% of the nights analysed. This analysis indicates that fan use can be recommended universally for effective cooling in northern Europe, northeastern regions of the USA, Canada, all of South America, and much of southeast Asia. However, fan use is often detrimental (ie, worsens heat stress) in exceptionally arid areas such as the Middle East or the southwestern regions of the USA, and on the hottest heatwave days in very humid regions such as northern India and parts of Pakistan. To enable the practical implementation of our findings, we propose revised simplified temperature thresholds for safe fan use of 39°C during the day for young adults, 38°C for older adults, and 37°C for older adults taking anticholinergic medications that impair sweating. Preferably, indoor temperatures should be directly measured with a thermometer to account for thermal differences between the indoor and outdoor environment. These new thresholds provide an evidence-based alternative to the existing 35°C threshold for fan use currently advised for all age groups by WHO, and substantially increase the number of days that fans can be recommended as a cooling device instead of air conditioning across many global regions.

Contributors

NBM, FG, and OJ designed the study. NBM, GKC, TE, FG, and MFBM did data analysis. NBM, GKC, TE, AC, and OJ interpreted the data. NBM and OJ accessed and verified the underlying data and take responsibility for the accuracy of this data. NBM, GKC, TE, AC, and OJ drafted the manuscript. All authors had full access to all data, edited and approved the final manuscript, and accept responsibility to submit for publication.

Declaration of interests

OJ reports funding from the National Health and Medical Research Council, Multiple Sclerosis Research Australia, and the Wellcome Trust. All other authors declare no competing interests.

Data sharing

Data for all metrics of interest, for each city, can be found in the appendix and are available for reuse, following proper citation to this original manuscript. For access and use of any additional data or materials, permission must be attained in writing from the corresponding author.

Acknowledgments

We thank Sarah Carter for producing figure 3.

Editorial note: the *Lancet* Group takes a neutral position with respect to territorial claims in published maps.

References

- 1 Semenza JC, Rubin CH, Falter KH, et al. Heat-related deaths during the July 1995 heat wave in Chicago. *N Engl J Med* 1996; **335**: 84–90.
- 2 Ostro B, Rauch S, Green R, Malig B, Basu R. The effects of temperature and use of air conditioning on hospitalizations. *Am J Epidemiol* 2010; **172**: 1053–61.
- 3 The Economist Intelligence Unit. The cooling imperative: forecasting the size and source of future cooling demand. <http://www.eiu.com/graphics/marketing/pdf/TheCoolingImperative2019.pdf> (accessed May 7, 2021).

- 4 Patz JA, Campbell-Lendrum D, Holloway T, Foley JA. Impact of regional climate change on human health. *Nature* 2005; **438**: 310–17.
- 5 Abel DW, Holloway T, Harkey M, et al. Air-quality-related health impacts from climate change and from adaptation of cooling demand for buildings in the eastern United States: an interdisciplinary modeling study. *PLoS Med* 2018; **15**: e1002599.
- 6 Davis LW, Gertler PJ. Contribution of air conditioning adoption to future energy use under global warming. *Proc Natl Acad Sci USA* 2015; **112**: 5962–67.
- 7 Shah N, Wei M, Letschert V, Phadke A. Benefits of leapfrogging to super efficiency and low global warming potential refrigerants in room air conditioning. October, 2015. <https://www.osti.gov/servlets/purl/1235571> (accessed May 6, 2021).
- 8 Jay O, Hoelzl R, Weets J, et al. Fanning as an alternative to air conditioning – a sustainable solution for reducing indoor occupational heat stress. *Energy Build* 2019; **193**: 92–98.
- 9 Anderson GB, Bell ML. Lights out: impact of the August 2003 power outage on mortality in New York, NY. *Epidemiology* 2012; **23**: 189–93.
- 10 United States Environmental Protection Agency. Excessive heat events guidebook. Washington, DC: United States Environmental Protection Agency, 2016. https://www.epa.gov/sites/production/files/2016-03/documents/ehguide_final.pdf (accessed May 31, 2018).
- 11 Centers for Disease Control and Prevention. Extreme heat. http://emergency.cdc.gov/disasters/extremeheat/heat_guide-page-2.asp (accessed June 18, 2015).
- 12 UK Government. Heatwave plan for England. May 13, 2014. <https://www.gov.uk/government/publications/heatwave-plan-for-england> (accessed July 16, 2015).
- 13 WHO. Heat-waves: risks and responses. Geneva: World Health Organization, 2004. <http://www.euro.who.int/en/publications/abstracts/heat-waves-risks-and-responses> (accessed June 24, 2015).
- 14 Gupta S, Carmichael C, Simpson C, et al. Electric fans for reducing adverse health impacts in heatwaves. *Cochrane Database Syst Rev* 2012; **7**: CD009888.
- 15 Hajat S, O'Connor M, Kosatsky T. Health effects of hot weather: from awareness of risk factors to effective health protection. *Lancet* 2010; **375**: 856–63.
- 16 Cramer MN, Jay O. Partitioned calorimetry. *J Appl Physiol* 2019; **126**: 267–77.
- 17 Morris NB, English T, Hospers L, Capon A, Jay O. The effects of electric fan use under differing resting heat index conditions: a clinical trial. *Ann Intern Med* 2019; **171**: 675–77.
- 18 Ravanelli NM, Hodder SG, Havenith G, Jay O. Heart rate and body temperature responses to extreme heat and humidity with and without electric fans. *JAMA* 2015; **313**: 724–25.
- 19 Inoue Y, Shibasaki M. Regional differences in age-related decrements of the cutaneous vascular and sweating responses to passive heating. *Eur J Appl Physiol Occup Physiol* 1996; **74**: 78–84.
- 20 Gagnon D, Romero SA, Cramer MN, et al. Age modulates physiological responses during fan use under extreme heat and humidity. *Med Sci Sports Exerc* 2017; **49**: 2333–42.
- 21 Gorup E, Rifel J, Petek Šter M. Anticholinergic burden and most common anticholinergic-acting medicines in older general practice patients. *Zdr Varst* 2018; **57**: 140–47.
- 22 Hou RH, Scaife J, Freeman C, Langley RW, Szabadi E, Bradshaw CM. Relationship between sedation and pupillary function: comparison of diazepam and diphenhydramine. *Br J Clin Pharmacol* 2006; **61**: 752–60.
- 23 National Centers for Environmental Information, National Oceanic and Atmospheric Administration. Global climate report—January 2020. <https://www.ncei.noaa.gov/sotc/global/202001> (accessed May 6, 2020).
- 24 UN Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2017 Revision. <https://www.un.org/development/desa/publications/world-population-prospects-the-2017-revision.html> (accessed May 25, 2021).
- 25 The Sun. Brits warned fans will make them hotter as mercury hits 35C. July 26, 2018. <https://www.thesun.co.uk/news/6872112/uk-heatwave-avoid-using-fans-dehydration/> (accessed Aug 11, 2020).
- 26 Ngarmpraprasert S, Koetsinchai W. The effect of air-conditioning on worker productivity in office buildings: a case study in Thailand. *Build Simul* 2010; **3**: 165–77.
- 27 Graham C, Morris NB, Harwood AE, Jay O. Ad libitum water consumption offsets the thermal and cardiovascular strain exacerbated by dehydration during a 3-h simulated heatwave. *Eur J Appl Physiol* 2020; **120**: 391–99.
- 28 Phil JF, Lundbye-Jensen J, Christiansen L, et al. High prevalence of hypohydration in occupations with heat stress: perspectives for performance in combined cognitive and motor tasks. *PLoS One* 2018; **13**: e0205321.
- 29 Sawka MN, Cheuvront SN, Kenefick RW. Hypohydration and human performance: impact of environment and physiological mechanisms. *Sports Med* 2015; **45** (suppl 1): S51–60.
- 30 Morris NB, Gruss F, Lempert S, et al. A preliminary study of the effect of dousing and foot immersion on cardiovascular and thermal responses to extreme heat. *JAMA* 2019; **322**: 1411–13.
- 31 Cramer MN, Huang M, Moralez G, Crandall CG. Keeping older individuals cool in hot and moderately humid conditions: wetted clothing with and without an electric fan. *J Appl Physiol (1985)* 2020; **128**: 604–11.
- 32 de'Donato FK, Stafoggia M, Rognoni M, et al. Airport and city-centre temperatures in the evaluation of the association between heat and mortality. *Int J Biometeorol* 2008; **52**: 301–10.
- 33 Ramamurthy P, González J, Ortiz L, Arend M, Moshary F. Impact of heatwave on a megacity: an observational analysis of New York City during July 2016. *Environ Res Lett* 2017; **12**: 054011.
- 34 Mandal J, Pu Y, Overvig AC, et al. Hierarchically porous polymer coatings for highly efficient passive daytime radiative cooling. *Science* 2018; **362**: 315–19.
- 35 Sakka A, Santamouris M, Livada I, Nicol F, Wilson M. On the thermal performance of low income housing during heat waves. *Energy Build* 2012; **49**: 69–77.
- 36 Intergovernmental Panel on Climate Change. Global warming of 1.5 C. https://www.ipcc.ch/site/assets/uploads/sites/2/2019/06/SR15_Full_Report_Low_Res.pdf (accessed May 7, 2021).
- 37 Coffel ED, Horton RM, de Sherbinin A. Temperature and humidity based projections of a rapid rise in global heat stress exposure during the 21st century. *Environ Res Lett* 2018; **13**: 014001.

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/350110404>

Role of Neuronal Guidance Cues in the Pathophysiology of Obesity: A Peripheral and Central Overview

Article in *Current Pharmaceutical Design* · March 2021
DOI: 10.2174/2381612824660213110394059

CITATION
1

READS
53

4 authors:



Daniela Inoue
São Paulo State University
27 PUBLICATIONS 458 CITATIONS

[SEE PROFILE](#)



Mohammad Fauzan Bin Maideen
The University of Sydney
5 PUBLICATIONS 84 CITATIONS

[SEE PROFILE](#)



Alberto Jiménez-Maldonado
Autonomous University of Baja California
51 PUBLICATIONS 255 CITATIONS

[SEE PROFILE](#)



Fabio Santos Lira
São Paulo State University
348 PUBLICATIONS 7,241 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



Análisis del consumo crónico de etanol en el desarrollo de un fenotipo similar al de la diabetes tipo 1 [View project](#)



Análisis del efecto del consumo crónico de alcohol en el desarrollo de resistencia a la insulina ligada a una posible alteración en los niveles de adiponectina en sangre. [View project](#)

All content following this page was uploaded by Alberto Jiménez-Maldonado on 09 September 2021.

The user has requested enhancement of the downloaded file.

REVIEW ARTICLE



Role of Neuronal Guidance Cues in the Pathophysiology of Obesity: A Peripheral and Central Overview



Daniela S. Inoue^{1*}, Mohammad F. Bin Maideen^{2,3}, Alberto Jiménez-Maldonado⁴ and Fábio S. Lira^{1,2}

¹Post-Graduation Program in Movement Sciences, Department of Physical Education, State University (Unesp), School of Technology and Sciences, Presidente Prudente, 19060-900, São Paulo, Brazil; ²The University of Sydney, School of Health Sciences, Faculty of Medicine and Health, NSW, Australia; ³The University of Sydney, Charles Perkins Centre, NSW, 2006, Australia; ⁴Facultad de Deportes Campus Ensenada, Universidad Autónoma de Baja California, Mexico

ARTICLE HISTORY

Received: August 18, 2020
Accepted: February 16, 2021

DOI:
10.2174/138161252466210316094659



CrossMark

Abstract: Obesity is associated with an exacerbated synthesis and secretion of several molecules, which culminates in chronic low-grade inflammation and insulin resistance. Such conditions affect molecular and physiological responses of several organs and, if not resolved, predispose the obese patients to other diseases such as Type 2 diabetes, atherosclerosis, cancer, neural injuries, and cognitive impairments. A microenvironment with an excess of pro-inflammatory cytokines released by different cells, including immune and adipose cells lead to metabolic and non-metabolic diseases during obesity. In this context, the role of neuronal guidance cues named netrin, semaphorin and ephrin is novel. Specifically, the available literature indicates that besides their classic role as molecules that guide the axon to its target site, the neuronal guidance cues exhibit immunomodulatory functions from adipose tissue to the neural environment. In the current narrative review, we discuss the participation of the neuronal guidance cues on the physiology and pathophysiology of obesity. We also discuss the feedback loop of obesity on the netrin, semaphorin and ephrin functions that impair the structure and function of the brain. The integrative view of the neuronal guidance cues can be relevant in designing new treatments focus on attenuating metabolic and immune disorders in obese patients and reduce the risk of acquiring diseases such as Type 2 diabetes, atherosclerosis, cancer, and neural injuries.

Keywords: Cell adhesion, cell migration, UNC5B, neuropilins, Eph receptors, hippocampus.

1. INTRODUCTION

The pathophysiology of obesity is closely related to genetical, behavioral and environmental interactions, which culminate in a positive energy balance that leads to excessive accumulation of lipids in adipocytes, generating morphological and functional changes in adipose tissue physiology [1, 2]. A marked presence of immune cells in adipose tissue has a great influence on the coordination of energy metabolism through the activation of pro-inflammatory pathways [1-3]. The chronic state of excess energy storage as well as the constant activation of pro-inflammatory pathways lead to a low-grade inflammation and systemic insulin resistance (IR), which overload all body systems and trigger the development of several conditions such as Type 2 diabetes, cancer, cardiovascular diseases and cognitive impairments [1-3]. More recent scientific and technological advances have uncovered other molecules involved in chronic low-grade inflammation and systemic IR. Between them are netrin, semaphorin and ephrin, known as neuronal guidance cues.

Neuronal guidance cues, when initially discovered in studies of embryogenesis, were considered as proteins responsible for guiding axons to interact with other neurons and organs of other systems, during the process of neural development [4, 5]. In this context, these guidance cues are localized in the extracellular matrix and have the capacity to attract or to repel axons in order to reach the target or avoid inappropriate sites, respectively [4, 5]. However in the last few decades, it has been shown that these molecules

also have functions outside the neural environment and have pleiotropic effects such as adhesion and migration of cells [4, 5].

Specifically, the neuronal guidance cues perform immunomodulatory functions from adipose tissue to the neural environment; the latter can be related to obesity [5-7]. In light of this, studies performed (*in vitro*, in rodents or humans) have shown that isoforms of neuronal guidance cues contribute to maintenance of the pro-inflammatory state of obesity and its comorbidities [5-7]. It is expected that this review supports the advancement of future studies related to the understanding the complexity of obesity, as well as assist in the development of new therapeutic strategies involving neuronal guidance cues responses.

2. NEURONAL GUIDANCE CUES - AN OVERVIEW

Directing the growth of axons (neurite) so that they reach their intended targets (another neuron or organ) during neural development is an already well-established function of the guidance cues. As the name suggests, neuronal guidance cues are molecules that give "cues" to where the neuron's branches should go until they reach their target. This action is linked to other cells such as glial cells, other types of neurons and even cells from other tissues such as epithelium and muscle, which are also capable of secreting these proteins [8]. The interaction between specific ligands and receptors triggers molecular signaling pathways that will culminate in neuronal projection, generating a structural configuration of the nervous system allowing it to function effectively [8].

Neuronal guidance cues consist of different families of molecules and each of these families has different subtypes with neuronal and non-neuronal functions, and specific receptors [5]. In this section, we will discuss the main roles of three molecular families, namely netrins, semaphorins and ephrins, whilst highlighting their interactions with pathophysiological conditions other than obesity.

* Address correspondence to these authors at the Universidade Estadual Paulista, UNESP, Rua Roberto Simonsen, 305, 19060-900, Presidente Prudente, São Paulo, Brazil; Tel: 55 18 3229-5906; Fax: 55 18 3229-5710; E-mail: dainoue@gmail.com; fabio.lira@unesp.br

2.1. Netrins

Netrins were the very first guidance cues discovered in the 1990s, and its name means ‘one who guides’, precisely because of its role in directing axonal outgrowth [9, 10]. There are several subtypes: uncoordinated-6 (UNC-6) [9, 10], netrin-A and netrin-B found in invertebrates [11], and netrin-1, netrin-2 [12], netrin-3 [13], netrin-4 [14, 15], netrin-G1 and netrin-G2 [16, 17] found in vertebrates and mammals. In terms of molecular structure, netrins are similar to laminin, a component of basal membrane of extracellular matrix [12]. Netrins are able to bind to different transmembrane receptors, which mediate intracellular responses. The main receptors are: deleted in colorectal cancer (DCC) [13], neogenin [13], down syndrome cell adhesion molecule (DSCAM) [18], all of which belong to the immunoglobulin family; uncoordinated locomotion-5 (UNC5) family composed by different subtypes such as UNC5A-D found in humans and UNC5H1-4 found in rodents [19], and $\alpha 6 \beta 4$ and $\alpha 3 \beta 4$ integrins [13, 20]. In addition, netrin receptors react in distinct ways; in the presence of netrin, positive signals arise, resulting in cell motility or axon outgrowth, and in the absence of netrin, negative signals result in apoptosis [21, 22].

Currently, netrin-1 is considered as ‘the classical guidance cue’, and its function seems to be dependent on the type of receptor and its possible combination with another receptor at the time of binding [23]. For instance, netrin-1 is able to bind to two DCCs, leading them to a homodimerization and triggers a signaling pathway which culminates in cell attraction, while binding to UNC5B associated with DCC might trigger repellent signaling pathways [21, 23]. According to the diversity of interactions between its receptors, netrin-1 displays a multitude of functions beyond the guiding of axons, which comprise of cell migration, adhesion, survival, angiogenesis and interaction with immune cells, not only in the nervous system but in different organs [5, 21].

A number of studies have proven the relationship between netrin-1 and the body's inflammatory process [24-27]. In detail, Madiero *et al.* [24] showed that the blockade of netrin-1/UNC5B reduced inflammation in the autoimmune disease of arthritis in mice models. On the other hand, netrin-1 concentration was related to an anti-inflammatory response in the study of Sun *et al.* [25], the concentrations of which was negatively related to interleukin-17 (IL-17) and positively related to interleukin-10 (IL-10), suggesting that lower netrin-1 expression might be related to increased neurotoxic amyloid beta (A β) peptides in rats with Alzheimer disease. In accordance with anti-inflammatory effects, Bruikman *et al.* [26] concluded that plasma netrin-1 could be associated with atherosclerosis initiation processes in humans, the concentrations of which were negatively correlated with arterial wall inflammation. According to Lin *et al.* [27], the anti-inflammatory function of netrin-1 is exhibited in its capacity to suppress Toll-like receptor-4 (TLR-4) and prevent nuclear factor kappa B (NFkB) activation in endothelial cells. Thus, netrin-1 seems to have a pleiotropic immunological function, sometimes potentiating and sometimes minimizing inflammatory effects, depending on the condition of the microenvironment and the type of tissue.

2.2. Semaphorin

Like netrins, semaphorins are a family of proteins which were discovered in the 1990s, when they were identified with neuronal guidance cue characteristics [5, 28, 29]. Initially, these proteins received different names and classifications in distinct laboratories, although they carried the same main protein structure - 500 amino acid extracellular domain, now known as ‘sema domain’. In 1998, the Semaphorin Nomenclature Committee [30], established a uni-

fied nomenclature: semaphorin (from the word ‘semaphore’ which means ‘an apparatus for signaling’). However, since these proteins differ in their structure anchorage, semaphorins have been differentiated into eight different classes (1-7 and V) and subclasses (capital letters according to specific classifications) [30]. Class 1 and 2 correspond to invertebrates, classes (subclasses) 3 (sema3A-G), 4 (sema4A-D), 6 (sema6A-D) and 7 (sema7A) correspond to vertebrates only, class 5 (sema5A-B) corresponds to both invertebrates and vertebrates, and class V correspond to viruses. The structural anchorage of semaphorin class 3 is a secreted type, while class 4 to class 6 is a transmembrane type, and class 7 is linked by a glycosylphosphatidylinositol anchor [5, 30]. Also, as an indication to humans, it is to be written as ‘SEMA’ (e.g., SEMA3E), whereas in mice/rat models, it is indicated as ‘sema’ (e.g., sema3E) [30]. Semaphorins, according to their class and subclass, trigger different effects, and these are dependent on their binding to different receptors as well. In mammals, the most common semaphorin receptor comprises the plexin family (divided into four classes, A-D). To some classes of semaphorin, a specific co-receptor, called neuropilins, which has two subtypes (Nrp1 and Nrp2), is necessary. Class 3 semaphorin (SEMA3), with the exception of subclass SEMA3E, must bind to neuropilin to activate the plexin receptor, while the other classes need only the plexin receptor to trigger signaling pathways [30]. The review of Worzfeld and Offermans [31] presents a detailed description of semaphorins and their receptors.

As neuronal guidance cues, semaphorins were initially recognized as having repellent effects during neural development [28, 29], however, recently, researchers demonstrated repellent and attractant roles in neural environments [32]. Additionally, more recent studies revealed the functions of these molecules outside of the nervous system. Concretely, several classes of semaphorins promote or inhibit vascular development [33], bone homeostasis [34] and tissue regeneration [33]. Other semaphorins, such as SEMA3A, SEMA3E and SEMA4A, interact with immune cells triggering inflammatory processes as autoimmune disorders [34] and tumor growth [31, 34]. Thus, the semaphorin family protein plays a considerable influence on pivotal whole-body function.

2.3. Ephrin

The discovery of this molecule occurred in 1987 through the identification of its receptors in studies related to oncogenic tyrosine kinase [35]. Eph receptors (from Erythropoietin-producing hepatocellular cell carcinoma cell line) are considered to be the largest family of neuronal guidance cues receptors, whose ligand has been named Ephrin (from Eph receptor interacting proteins) [36, 37]. Like netrins and semaphorins, ephrin ligands and receptors are divided into classes (subclasses): Ephrin-A (A1-A5) and Ephrin-B (B1-B3) ligands, and Eph-A receptors (A1-A8 and A10) and Eph-B (B1-B3), respectively [36, 37]. Although they belong to the same family of neuronal guidance cues, the ligands Ephrin-A and Ephrin-B differ greatly in their structures [36]. Ephrin-As is smaller in size with a binding domain attached to the plasma membrane via a glycosylphosphatidylinositol anchor. Ephrin-Bs, however, have a transmembrane protein complex [36, 37]. The structures of the EphA and EphB receptors are similar, with intracellular, transmembrane regions and an extracellular binding domain. As it is a tyrosine kinase receptor, it is dependent on phosphorylation to continue intracellular signaling after its activation [36, 37].

The binding of the ephrin-eph receptor axis occurs via direct structural contact between cells; that is, the ephrins anchored in a cell membrane ‘fit’ directly to the anchored receptors of the neighboring cell, triggering forward and reverse signals [36]. Pasquale

Table 1. Subtypes of Netrin, Semaphorin and Ephrin and their receptors types in vertebrates.

NETRIN			Refs.
-	Class	Subclass	-
Subtypes	netrin-1	-	[12]
	netrin-2	-	[12]
	netrin-3	-	[12]
	netrin-4	-	[14, 15]
	netrin-G	netrin-G1, netrin-G2	[16, 17]
Receptors types	DCC	-	[13]
	Neogenin	-	[13]
	DSCAM	-	[18]
	UNC5 (human)	UNC5A; UNC5B; UNC5C; UNC5D	[19]
	UNC5H (rodents)	UNC5H1; UNC5H2; UNC5H3; UNC5H4	[19]
	Integrins	$\alpha 6 \beta 4$; $\alpha 3 \beta 4$	[13, 20]
SEMAPHORIN			-
-	Class	Subclass	-
Subtypes	Sema3	Sema3A; Sema3B; Sema3C; Sema3D; Sema3E; Sema3F; Sema3G	[30]
	Sema4	Sema4A; Sema4B; Sema4C; Sema4D	[30]
	Sema6	Sema6A; Sema6B; Sema6C; Sema6D	[30]
	Sema7	Sema7A	[30]
Receptors types	Plexin	PlexinA; PlexinB; PlexinC; PlexinD	[30]
	Neuropilin (Nrp)	Nrp-1; Nrp-2	[30]
EPHRIN			-
-	Class	Subclass	-
Subtypes	EphrinA1-5	EphrinaA1; EphrinaA2; EphrinaA3; EphrinaA4; EphrinaA5	[36, 37]
	Ephrin-B1-3	Ephrin-B1; Ephrin-B2; Ephrin-B3	[36, 37]
Receptors types	Eph-A1	Eph-A1; Eph-A2; Eph-A3; Eph-A4; Eph-A5; Eph-A6; Eph-A7; Eph-A8; Eph-A10	[36, 37]
	Eph-B1-3	Eph-B1; Eph-B2; Eph-B3	[36, 37]

Abbreviations: DCC: deleted in colorectal cancer; DSCAM: down syndrome cell adhesion molecule; UNC-5: uncoordinated locomotion-5; Sema: semaphorin; Nrp-1: Neuropilin-1; Nrp-2: Neuropilin-2; Eph: Erythropoietin-producing hepatocellular cell carcinoma cell line. Ref.: references.

[37] listed several functions of ephrins and their receptors activation, as actions related to cell shape, movement, survival, proliferation and differentiation. During embryonic development, these molecules have the important function of neural structure organization, displaying both repellent and attractant actions, with the occasional boundary formation [36]. In summary, Ephrin-eph signaling has a pleiotropic function, not only in neural development, but in adult life and in different conditions such as nervous system regeneration and cancer development. Table 1 shows a summary of subtypes of netrin, semaphorin and ephrin and their types of receptors.

3. PATHOPHYSIOLOGY OF OBESITY AND THE PARTICIPATION OF NEURONAL GUIDANCE CUES

Obesity is a complex pathophysiological condition that involves different body system interactions simultaneously, directly influenced by environmental and behavioral aspects [1, 2]. Biologically, obesity is much more than an excessive accumulation of fat since it is well established that adipose tissue is a metabolically active organ that influences the neuroendocrine control of the body's energy balance, and in parallel, it is able to trigger resistance to systemic insulin, a precursor to several chronic degenerative diseases [1-3].

The protagonism of adipokines and cytokines has been increased in studies of obesity and its comorbidities. The discovery of leptin [38] and the recognition of metabolic inflammation in adipose tissue [3] opened up a range of possibilities for the action of several other molecules to be explored in the condition of obesity. One of the cell categories is the neuronal guidance cues, which, as

we briefly described in the previous section, have been linked to immune responses, in addition to their more classical function in the development of the nervous system. Next, we will discuss the participation of neuronal guidance cues in the onset and maintenance of the pathophysiological condition of obesity.

3.1. Genetic Issues

The genetic influence on body mass involves types of gene variants, their frequency of appearance in the population as well as effect sizes of the phenotype. 'Common' variants are found at a frequency of the minor allele of more than 5% in a population and generally exerts a modest effect size on body mass, while 'intermediate' variants (1% to 5%) exert a moderate impact and 'rare' variants (<1%), although found at lower frequencies, are associated with more severe obesity [39]. The relationship between genetic factors and obesity can be explored primarily from three obesity subtypes: syndromic, non-syndromic monogenic (or Mendelian) and polygenic [40].

Monogenic obesity is caused by a single gene, with a larger effect size in the development of obesity [40]. The Mendelian form of obesity refers to chromosomal abnormalities and rare pathogenic variants in genes encoding key proteins in the regulation of energy balance [40]. Syndromic Mendelian obesity is accompanied by congenital abnormalities that affect specific organs, along with intellectual impairments, such as Prader-Willi syndrome. Non-syndromic Mendelian obesity is characterized by mutations in the genes related to energy homeostasis signaling pathways controlled by a neural circuit [40].

This neural circuit, also known as the melanocortin circuit, is localized in the hypothalamus, involving leptin-responsive neurons, which produce anorexigenic (e.g. pro-opiomelanocortin - POMC) or orexigenic (e.g. neuropeptide Y/Agouti-related protein) signalers [41]. When the POMC signaling pathway is activated, its neurons release α -melanocyte-stimulating hormone (α -MSH) which bind to melanocortin-4 receptor (MC4R), inducing satiety and increasing energy expenditure [41]. During pre-natal and post-natal brain development, all subclasses of SEMA3 form part of the proteins responsible for generating neural connections in the melanocortin circuit [41].

According to a recent study by van de Klaauw *et al.* [41], there are 40 rare variants in 13 genes of the SEMA3 family and their receptor genes related to the early onset of severe obesity in humans. Also, the authors found evidence in zebrafish and mice that deletion of some class 3 semaphorin genes and genes related to co-receptor neuropilin in POMC neurons might result in augmented adiposity and contribute to the reduction of energy expenditure and weight gain, respectively. These mutations of SEMA3s seem to impair the secretion and signaling pathways during the development of the melanocortin circuit, and consequently modulating the energy balance homeostasis [41]. These findings concerning mutations in the melanocortin circuit have relevance on the understanding of human hypothalamus development and the onset of severe obesity in childhood and are considered as milestones to future studies related to the understanding of non-syndromic monogenic obesity [42].

In polygenic obesity, there are changes in multiple genes, however, modest effects of each individual gene result in a greater predisposition to increased fat accumulation [40]. Wolf *et al.* [43] had suggested the possible participation of semaphorin on the innervation of brown adipose tissue in mice, in which macrophage mutation could result in overexpressed plexin receptor, contributing to the repulsion of sema6A-expressing sympathetic nerve, affecting thermogenesis responses and weight maintenance. Further studies are needed to clarify the relation between sympathetic innervation, brown adipose tissue, thermogenesis and weight control.

3.2. White Visceral Adipose Tissue

White adipose tissue (WAT) has the primary function of storing energy through large-scale accumulation of free fatty acids and glycerol which form triacylglycerol, and its adipocytes contain a large single drop of fat that "pushes" the nucleus and all organelles close to plasma membrane [44]. Adipose tissue, in general, is a structure formed by several types of cells, most parts corresponding to adipocytes, and other parts formed by stromal-vascular fractions that include connective tissue cells, smooth muscle, nerves, immune cells, pre-adipocytes, among others [44]. All of them are joined by collagen fibers presented in the extracellular matrix (ECM). The ECM provides mechanical and physiological support *via* remodeling itself through biochemical responses, as weight gain or loss is demonstrated in the individual [45]. Together, all cells that comprise the WAT are major secretors of chemical signals that act in an autocrine, paracrine and endocrine manner, and in obesity, WAT is considered a pivotal endocrine organ [44].

A study carried out by Mejhert *et al.* [46] identified SEMA3C in subcutaneous WAT obtained from human individuals. Its expression and secretion seem to be more prevalent in adipocytes and was correlated with hypertrophy of WAT and whole-body IR. In addition, the authors found SEMA3C responsible for stimulating pre-adipocytes (major cellular mediators promoting WAT fibrosis deposition in pro-inflammatory microenvironment of obesity) to express genes of proteins related to remodeling ECM, as fibronectin

and elastin, matricellular factors, as interleukin-6 (IL-6), as well as finding a correlation between SEMA3C and the fibrosis of ECM of WAT. This study suggests the neuronal guidance cue SEMA3C as a potential adipokine with pro-inflammatory responses. The location of WAT is crucial for pathophysiological development of obesity. White visceral adipose tissue (VAT), one that wraps and protects organs against mechanical impact, is more metabolically active, with greater innervation and blood supply, facilitating the entry and exit of nutrients, chemical signalers and immune cells from the whole body. Several studies confirm that VAT is a potential site that triggers metabolic disorders present in obesity [44, 47].

The abilities to store energy and fight infection are considered as essential survival mechanisms in complex (multicellular) organisms, as seen in humans. In addition, these two abilities work together [48], and this becomes evident in the pathophysiology of obesity. On one hand, the positive energy balance that leads to excessive accumulation of fat (energy storage) that culminates in adipocyte hypertrophy generates morphological and functional changes in WAT [34]. On the other hand, the marked presence of immune cells in VAT has a great influence on the coordination of energy metabolism through the activation of pro-inflammatory pathways by bacterial fragments from the intestinal microbiota and/or saturated fatty acids in fighting infection [3, 49, 50].

Hypertrophied adipocytes can disrupt blood supply in some parts of VAT, leading to hypoxia [51]. This morphophysiological condition alters the VAT steady-state triggering several mechanisms to rectify the blood deficit, including the production of pro-inflammatory cytokines, as tumor necrosis factor- α (TNF- α) and IL-6, by resident immune cells to stimulate lipolysis of hypertrophied adipocyte and in some cases, its apoptosis [51]. Simultaneously, adipocytes release chemoattractant proteins to aid in the infiltration of new leukocytes to reinforce the fight for immunometabolic balance restoration [51]. In this context, there is a participation of neuronal guidance cues.

Regarding leukocyte infiltration, even though it is known that monocytes largely express chemokine ligand 2 (CCL2) receptors, also known as monocyte chemoattractant protein-1 (MCP-1), to stimulate the infiltration of these cells from the bloodstream to VAT, semaphorins have been identified to demonstrate a similar function too [52]. Sema3E, previously recognized for its repellent function, seems to be the largest recruiter of macrophages among the class 3 semaphorins, as demonstrated by Shimizu *et al.* [52]. In their study, obese mice fed with a high-fat diet presented with a higher blood concentration of Sema3E, higher expression of Sema3e in adipocytes, and its receptor (plexinD1) was found in both adipocytes and macrophages while the deletion of Sema3e gene improved the immunometabolic profile. In addition, Sema3E-dimers plexinD1/Nrpl axis was found to be an important key regulator of adipose tissue inflammation and IR since Sema3E was able to activate p38MAPK and inhibit the Akt phosphorylation [52]. Studies in human models are necessary to confirm if class 3E semaphore binding to plexinD1 would mimic the mice model findings.

If, on one hand, some guidance cues act to attract macrophages, on the other hand, other guidance cues can also promote their retention in VAT. Ramkhalawon *et al.* [6] discovered that netrin-1 promotes macrophage accumulation in adipose tissue through higher expression of this guidance cue and its repellent receptor, UNC-5b, in obese mice and humans when compared to respective lean control groups. In addition, this high expression of Netrin-1 and Unc-5b in adipose tissue was associated with the expression of IL-6 and Tnf- α . They also found that netrin-1 impaired macrophage emigration from adipose tissue by low responsiveness to CCL9, a chemokine to guide macrophages from tissues to lymph

nodes. A subsequent study from the same research group showed that the deficiency of netrin-1 in cells derived from bone marrow was able to reduce the accumulation of macrophages in adipose tissue with consequent improvement in insulin sensitivity [53]. Altogether, these studies reinforce that netrin-1 has a role in sustaining macrophage presence in VAT and, therefore, contributes to immunometabolic disorders.

Ephrin also appears to have a role in obesity. When ephrin-B1 was identified in immune cells present in atherosclerosis lesions and having a role in downregulating migration of macrophages by inhibition of MCP-1, Mori *et al.* [54] investigated the possible functions of Ephrin-B1 in obesity. The authors found negative correlations between mRNA expression of Ephrin-B1 with estimated visceral adipose tissue area, lower expression of Ephrin-B1 in adipose tissue of diet-induced obese mice, and a reduced expression of this guidance cue when under stimulation of TNF- α in cultured 3T3-L1 adipocyte. It was also found that Ephrin-B1 from adipose tissue inhibited macrophage adhesion to adipocytes. The previous findings support a link among Ephrin-B1 and a reduction of the chronic low-grade inflammation.

3.3. Comorbidities of Obesity and Neuronal Guidance Cues

Chronic low-grade inflammation and systemic IR negatively impact both peripheral and central functions [1, 2]. In regard to this, recent studies highlighted the role of neuronal guidance cues in these conditions [8, 55, 56]. IR and hyperinsulinemia are a risk factor for renal injury. Övünç Hacıhamdioğlu *et al.* [55] identified the potential role of netrin-1 in kidney injury in children with obesity. They found higher netrin-1 concentration in urine in the obese group and reported that these individuals may have increased netrin-1 production in the endothelial cells of the kidneys. Based on their results, the authors suggested urinary netrin-1 as a promising early biomarker of kidney injury with tubular damage.

Besides the negative impact of obesity on peripheral organs, there is conclusive evidence that indicate the negative impact of obesity on the function and structure of the central nervous system [57]. For example, the study of Yau *et al.* [58] found that in adolescents with metabolic syndrome, there was a relationship between smaller hippocampal size and lesser cerebrospinal fluid, and a lower academic and attention performance. Metabolic inflammation present in obesity seems to influence the permeability of the blood brain barrier, changing the input and output of different types of proteins, including pro-inflammatory, which alter the neural environment to a neuroinflammation state which impairs its function [59] and may trigger an inflammatory metabolic neural disease, such as Alzheimer's disease [57].

According to a review by Lee *et al.* [8], the authors suggested there are antagonistic effects of netrin depending on conditions, for example, in experiments investigating neurological diseases models netrin-UNC5 axis has an anti-inflammatory role and a neuroprotective function, while in primary cultured human endothelial cells, the signaling pathway seems to trigger TNF- α and interferon- γ , pro-inflammatory proteins present in neuroinflammation conditions. In addition, netrin-1 reduced the production of beta-amyloid, and in the presence of mutation, increased neuronal death in the hippocampus was observed. Semaphorins also play a part in neuroinflammation, for example, Semaphorin 4D as attenuating lipopolysaccharide-stimulated pro-inflammatory responses in glia cells [8]. Lipopolysaccharide is a Gram-negative bacterial fragment that is able to trigger pro-inflammatory cytokine production, and its blood concentration is commonly high in obesity, aggravating immunometabolism dysfunction [49]. Table 2 summarizes responses of neuronal guidance in obesity.

Table 2. Neuronal guidance cues in obesity context.

Neuronal Guidance Cues	Effects in Obesity	Refs.
Netrin-1	Accumulation of macrophage	[6]
	Expression of IL-6 and TNF- α	[6]
	Low concentrations improve insulin sensibility	[53]
	Early biomarker of kidney injury with tubular damage	[55]
	Reduction of beta-amyloid production	[8]
	Mutation increases neuronal death in hippocampus	[8]
SEMA3 classes	Rare genetic variants related to early onset of severe obesity	[41]
	Mutations impair energy balance homeostasis	[41]
Sema6A	Mutations affect thermogenesis and weigh maintenance	[43]
SEMA3C	Hypertrophy of WAT and whole-body IR	[46]
	Fibrosis of ECM of WAT	[46]
Sema3E	Recruiter of macrophages	[52]
	Activate p38MAPK and inhibit Akt phosphorylation	[52]
Sema4D	Attenuating lipopolysaccharide-stimulated pro-inflammatory responses	[8]
Ephrin-B1	Anti-inflammatory properties	[54]
	Inhibition of MCP-1	[54]
	Negative correlation with visceral fat area	[54]
	Inhibition of macrophage adhesion to adipocytes	[54]

Abbreviations: IL-6: Interleukine 6; TNF- α : Tumor necrosis factor-alpha; WAT: white adipose tissue; IR: insulin resistance; ECM: extracellular matrix; MCP-1: monocyte chemoattractant protein-1.

In addition, maternal obesity has been found to be detrimental to offspring health in several ways. A study by Sanders *et al.* [56] showed that maternal obesity impairs orexigenic NPY neuronal circuit development in mice offspring as the high concentrations of pro-inflammatory cytokine IL-6 seem to impair the connection of NPY neurons in arcuate nucleus (ARC) with neurons of paraventricular nucleus (PVN) in the hypothalamus during the fetal period. The authors detected netrin-1 as a protein responsible for guiding axons of ARC to PVN, however, IL-6 could be related to alterations of receptor DCC and disrupting netrin-1 function as an axonal guidance cue. Unc-5 gene was also found to be modulated by maternal obesity; however, IL-6 was not identified as responsible for this modulation, suggesting the possibility of other inflammatory proteins to act on netrin-1-UNC-5 axis in the hypothalamic development of mice offspring with obese mothers. The impact of the low neuron projection between these two areas of the hypothalamus could impact orexigenic abilities; however, more studies are necessary to investigate its real impact on body mass maintenance of offspring.

4. SYNAPSES LOSS IN THE HIPPOCAMPUS SECONDARY TO OBESITY

The previous section of the review discussed the impact of obesity on molecules that regulate neuronal guidance (*e.g.* netrins, semaphorin and ephrin families). However, another aspect that should be considered for obesity is that it is a morbid condition that induces total or partial loss of communication among previously well-established cell connections. The present section will discuss the available literature that explains the impact of obesity or metabolic syndrome (MetS) on the loss of synapses in the hippocampus. The information argued in the current section was obtained from rodent models [60-65].

The hippocampus is a member of the limbic system [66, 67], composed of three principal areas: hippocampus proper (cornu ammonis -CA-), dentate gyrus (DG) and the subiculum (including entorhinal area) [66, 67] (see [68] for more details). The neuronal

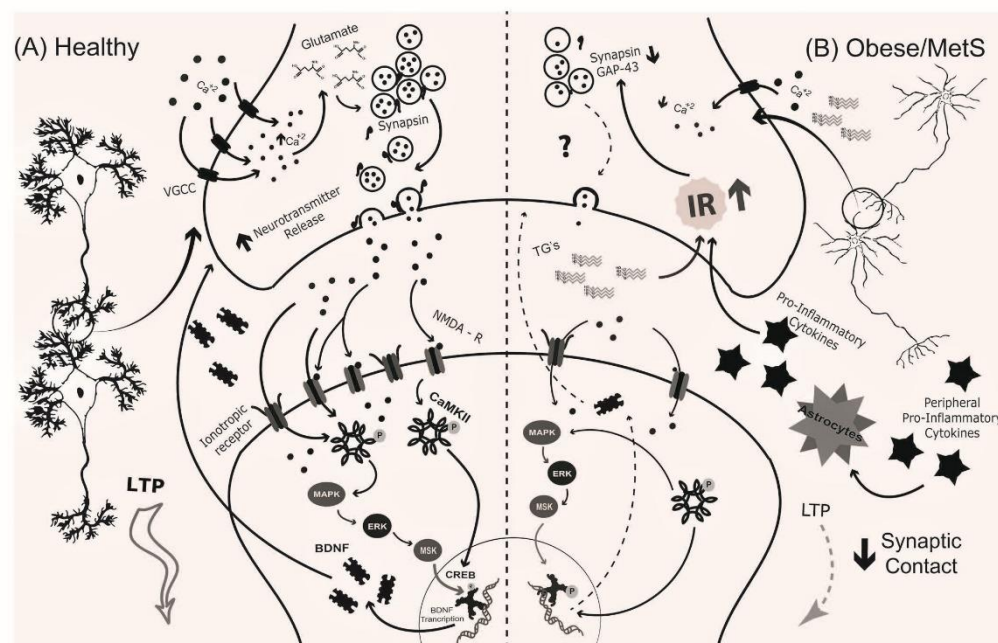


Fig. (1). Simplified model illustrating the impact of obesity and metabolic syndrome (MetS) on synapse loss at the hippocampal region. Under healthy conditions (left side **A**), the electrical signal generates an action potential (AP) in the presynaptic neuron. During the AP, the voltage gated calcium channels (VGCC) are activated allowing the flow of calcium (Ca^{2+}) into the intracellular region. The major Ca^{2+} levels induce the secretion of glutamate (through storage vesicles mobilization, a molecular process performed partially by synapsin). Once released, the glutamate binds and activate the NMDA receptors (mainly during long-term potentiation) localized in the dendritic spines of postsynaptic neurons. The ionotropic receptors allow the Ca^{2+} entry into the cytosol and activates several kinases, including the calcium/calmodulin-dependent protein kinase II (CaMKII). The CaMKII phosphorylates and activates to transcription factors such as cAMP response element-binding protein (CREB). Finally, CREB enhances the Bdnf transcription. The BDNF is a key molecule to strengthen LTP and synaptic plasticity (**A**). Obesity and MetS is a morbid condition (right side **B**) characterized by induced chronic low-grade inflammation at the periphery and neuroinflammation. The neuroinflammation induces synaptic damages and dendritic spine reduction (upper right). On the other hand, it has been hypothesized that during obesity and MetS peripheral molecules such as triglycerides (TGs) reach the hippocampus, to reduce the Ca^{2+} currents and induce insulin resistance (IR) (mid-center, right side). The last condition reduces the expression of genes associated with cognition and synaptic plasticity such as synapsin and GAP-43. Finally, a reduction in the synaptic contact during the MetS was also demonstrated, however, the molecular mechanism underlying this detriment has not been elucidated.

connectivity (synapses) present in the hippocampal region is associated with cognitive process (e.g. learning and memory) [66, 68]. Two main classes of neurons are preponderant in the hippocampus: inhibitory cells (GABAergic cells) ($\approx 10\text{-}20\%$ of the hippocampal neurons) and excitatory cells (glutamatergic cells) [69, 70]. Particularly, the glutamatergic synapses are linked with either learning and memory [67, 71, 72] or with memory consolidation, a neurophysiological process termed long-term potentiation (LTP) that represents the synapses' strength and efficiency of synaptic transmission [67, 73]. In brief, the pre-synaptic glutamatergic neuron releases the neurotransmitter glutamate as a consequence of an increase in intracellular calcium (Ca^{2+}) levels. Once released, glutamate binds to specific post-synaptic receptors (localized in dendrites spines), particularly ionotropic glutamate receptors (NMDA, AMPA,

Kinate receptor) and metabotropic receptors [68]. The activation of these receptors elevates the intracellular Ca^{2+} in the post-synaptic neuron that activates several signaling pathways, including calcium/calmodulin-dependent protein kinase II (CaMKII) [69, 73]. CaMKII phosphorylates and activates transcription factors such as cAMP response element-binding protein (CREB). Finally, CREB enhances the brain-derived neurotrophic factor (BDNF) gene transcription. The BDNF is a key molecule that enhances LTP and synaptic plasticity [74-76] (Fig. 1A), generating a positive feedback to improve cognition.

During obesity or MetS, the deficient neuronal connectivity reduces the LTP resulting in a detriment of the cognitive performance [64]. One of the mechanisms to impair the synapses is through the IR in the hippocampus [65, 77]. The IR generates a re-

duction in the spine dendrites [65]; and further downregulates the expression of proteins associated with neurotransmitter secretion (e.g. synapsin) [60, 77, 78], and molecules responsible for axon growth e.g. GAP-43, a relevant mechanism for the synaptic plasticity [78-80]. Finally, other authors reported negative effects of MetS on glutamate receptor levels and synaptic contact [64]; however, the authors did not explore the molecular mechanism released by the MetS to disrupt neuronal circuits in the hippocampal region. Nevertheless, they hypothesized that the peripheral molecules present during obesity and MetS (e.g. triglycerides) could reach the brain and provoke neuronal disorders, and reduce cognitive performance [64] (Fig. 1B).

CONCLUSION AND PERSPECTIVES

The current narrative review aimed to draft an overview of what has already been known about the role of neuronal guidance cues in the pathophysiology of obesity. Here, we focused on netrin, semaphorin and ephrin families and their respective receptors and influence on the metabolic inflammatory aspect of obesity. The current work discussed a noticeable and complex network of molecular communications, and inter- and intracellular responses that are still not completely recognized to be linked to obesity. Therefore, more studies are necessary to elucidate the potential role of neuronal guidance cues in the obesity and its comorbidities as MetS. Thus, we suggest advances in the interaction of different areas of biology research to cover several gaps between neuronal guidance cues and obesity issues, including the effects of different types of treatments in obesity. Future research might clarify the outcomes regarding pharmacological and non-pharmacological approach in relation to neuronal guidance cues and obesity. Thus, the current review article can be considered as a background for future scientific studies focused on elucidating the crosstalk between obesity and neuronal guidance cues in all biological spheres.

LIST OF ABBREVIATIONS

AMPA	= α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptor
ARC	= Neurons in Arcuate Nucleus
A β	= Amyloid Beta
BDNF	= Brain-derived Neurotrophic Factor
CA	= Cornu Ammonis
CaMKII	= Calcium/Calmodulin-dependent Protein Kinase II
CCL	= Chemokine Ligand
CREB	= cAMP Response Element-binding
DCC	= Deleted in Colorectal Cancer
DG	= Dentate Gyrus
DSCAM	= Down Syndrome Cell Adhesion Molecule
ECM	= Extracellular Matrix
Eph	= Erythropoietin-producing Hepatocellular Cell Carcinoma Cell Line
IL	= Interleukin
IR	= Insulin Resistance
LTP	= Long-term Potentiation
MC4R	= Melanocortin-4 Receptor

MCP-1	= Chemoattractant Protein-1
MetS	= Metabolic Syndrome
α -MSH	= α -Melanocyte-stimulating Hormone
NFKB	= Nuclear Factor Kappa B
NMDA	= N-methyl-D-aspartate receptor
NPY	= Neuropeptide Y
Nrp	= Neuropilins
POMC	= Pro-opiomelanocortin
PVN	= Paraventricular Nucleus
Sema	= Semaphorin
TLR-4	= Toll-like receptor-4
TNF- α	= Tumor Necrosis Factor- α
UNC-6	= Uncoordinated-6
UNC5	= Uncoordinated Locomotion-5
VAT	= Visceral Adipose Tissue
VGCC	= Voltage Gated Calcium Channels
WAT	= White Adipose Tissue

AUTHORS' CONTRIBUTIONS

"Conceptualization, Daniela S. Inoue; writing - original draft preparation, Daniela S. Inoue, Alberto Jiménez-Maldonado; writing - review and editing, Mohammad F. Bin Maideen; visualization, Alberto Jiménez-Maldonado; supervision, Fábio S. Lira. All authors have read and agreed to the published version of the manuscript.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors thank Patricia C. García-Suárez from Facultad de Deportes, Universidad Autónoma de Baja California, Ensenada, Mexico for construction of Figure 1.

REFERENCES

- [1] Gadde KM, Martin CK, Berthoud HR, Heymsfield SB. Obesity: Pathophysiology and management. *J Am Coll Cardiol* 2018; 71(1): 69-84. <http://dx.doi.org/10.1016/j.jacc.2017.11.011> PMID: 29301630
- [2] Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. *N Engl J Med* 2017; 376(3): 254-66. <http://dx.doi.org/10.1056/NEJMra1514009> PMID: 28099824
- [3] Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. *Nature* 2017; 542(7640): 177-85. <http://dx.doi.org/10.1038/nature21363> PMID: 28179656
- [4] Hinck L. The versatile roles of "axon guidance" cues in tissue morphogenesis. *Dev Cell* 2004; 7(6): 783-93.

- <http://dx.doi.org/10.1016/j.devcel.2004.11.002> PMID: 15572123
- [5] Feinstein J, Ramkhalawon B. Netrins & Semaphorins: Novel regulators of the immune response. *Biochim Biophys Acta Mol Basis Dis* 2017; 1863(12): 3183-9.
<http://dx.doi.org/10.1016/j.bbadis.2017.09.010> PMID: 28918114
 - [6] Ramkhalawon B, Hennessy EJ, Ménager M, *et al.* Netrin-1 promotes adipose tissue macrophage retention and insulin resistance in obesity. *Nat Med* 2014; 20(4): 377-84.
<http://dx.doi.org/10.1038/nm.3467> PMID: 24584118
 - [7] Yimer EM, Zewdie KA, Hishe HZ. Netrin as a novel biomarker and its therapeutic implications in diabetes mellitus and diabetes-associated complications. *J Diabetes Res* 2018; 8250521.
<http://dx.doi.org/10.1155/2018/8250521>
 - [8] Lee WS, Lee WH, Bae YC, Suk K. Axon guidance molecules guiding neuroinflammation. *Exp Neurobiol* 2019; 28(3): 311-9.
<http://dx.doi.org/10.5607/en.2019.28.3.311> PMID: 31308791
 - [9] Hedgecock EM, Culotti JG, Hall DH. The unc-5, unc-6, and unc-40 genes circumscribe migrations of pioneer axons and mesodermal cells on the epidermis in *C. elegans*. *Neuron* 1990; 4(1): 61-85.
[http://dx.doi.org/10.1016/0896-6273\(90\)90444-K](http://dx.doi.org/10.1016/0896-6273(90)90444-K) PMID: 2310575
 - [10] Ishii N, Wadsworth WG, Stern BD, Culotti JG, Hedgecock EM. UNC-6, a laminin-related protein, guides cell and pioneer axon migrations in *C. elegans*. *Neuron* 1992; 9(5): 873-81.
[http://dx.doi.org/10.1016/0896-6273\(92\)90240-E](http://dx.doi.org/10.1016/0896-6273(92)90240-E) PMID: 1329863
 - [11] Harris R, Sabatelli LM, Seeger MA. Guidance cues at the *Drosophila* CNS midline: identification and characterization of two *Drosophila* Netrin/UNC-6 homologs. *Neuron* 1996; 17(2): 217-28.
[http://dx.doi.org/10.1016/S0896-6273\(00\)80154-3](http://dx.doi.org/10.1016/S0896-6273(00)80154-3) PMID: 8780646
 - [12] Serafini T, Kennedy TE, Galko MJ, Mirzayan C, Jessell TM, Tessier-Lavigne M. The netrins define a family of axon outgrowth-promoting proteins homologous to *C. elegans* UNC-6. *Cell* 1994; 78(3): 409-24.
[http://dx.doi.org/10.1016/0092-8674\(94\)90420-0](http://dx.doi.org/10.1016/0092-8674(94)90420-0) PMID: 8062384
 - [13] Wang H, Copeland NG, Gilbert DJ, Jenkins NA, Tessier-Lavigne M. Netrin-3, a mouse homolog of human NTN2L, is highly expressed in sensory ganglia and shows differential binding to netrin receptors. *J Neurosci* 1999; 19(12): 4938-47.
<http://dx.doi.org/10.1523/JNEUROSCI.19-12-04938.1999> PMID: 10366627
 - [14] Yin Y, Sanes JR, Miner JH. Identification and expression of mouse netrin-4. *Mech Dev* 2000; 96(1): 115-9.
[http://dx.doi.org/10.1016/S0925-4773\(00\)00369-5](http://dx.doi.org/10.1016/S0925-4773(00)00369-5) PMID: 10940631
 - [15] Koch M, Murrell JR, Hunter DD, *et al.* A novel member of the netrin family, β -netrin, shares homology with the β chain of laminin: identification, expression, and functional characterization. *J Cell Biol* 2000; 151(2): 221-34.
<http://dx.doi.org/10.1083/jcb.151.2.221> PMID: 11038171
 - [16] Meerabux JM, Ohba H, Fukasawa M, *et al.* Human netrin-G1 isoforms show evidence of differential expression. *Genomics* 2005; 86(1): 112-6.
<http://dx.doi.org/10.1016/j.ygeno.2005.04.004> PMID: 15901489
 - [17] Aoki-Suzuki M, Yamada K, Meerabux J, *et al.* A family-based association study and gene expression analyses of netrin-G1 and -G2 genes in schizophrenia. *Biol Psychiatry* 2005; 57(4): 382-93.
<http://dx.doi.org/10.1016/j.biopsych.2004.11.022> PMID: 15705354
 - [18] Ly A, Nikolaev A, Suresh G, Zheng Y, Tessier-Lavigne M, Stein E. DSCAM is a netrin receptor that collaborates with DCC in mediating turning responses to netrin-1. *Cell* 2008; 133(7): 1241-54.
<http://dx.doi.org/10.1016/j.cell.2008.05.030> PMID: 18585357
 - [19] Thiebault K, Mazelin L, Pays L, *et al.* The netrin-1 receptors UNC5H are putative tumor suppressors controlling cell death commitment. *Proc Natl Acad Sci USA* 2003; 100(7): 4173-8.
<http://dx.doi.org/10.1073/pnas.0738063100> PMID: 12655055
 - [20] Yebra M, Montgomery AM, Diaferia GR, *et al.* Recognition of the neural chemoattractant Netrin-1 by integrins $\alpha 6 \beta 4$ and $\alpha 3 \beta 1$ regulates epithelial cell adhesion and migration. *Dev Cell* 2003; 5(5): 695-707.
[http://dx.doi.org/10.1016/S1534-5807\(03\)00330-7](http://dx.doi.org/10.1016/S1534-5807(03)00330-7) PMID: 14602071
 - [21] Cirulli V, Yebra M. Netrins: beyond the brain. *Nat Rev Mol Cell Biol* 2007; 8(4): 296-306.
<http://dx.doi.org/10.1038/nrm2142> PMID: 17356579
 - [22] Nakayama H, Kusumoto C, Nakahara M, Fujiwara A, Higashiya S. Semaphorin 3F and Netrin-1: the novel function as a regulator of tumor microenvironment. *Front Physiol* 2018; 9: 1662.
<http://dx.doi.org/10.3389/fphys.2018.01662> PMID: 30532711
 - [23] Boyer NP, Gupton SL. Revisiting netrin-1: one who guides (axons). *Front Cell Neurosci* 2018; 12: 221.
<http://dx.doi.org/10.3389/fncel.2018.00221> PMID: 30108487
 - [24] Mediero A, Wilder T, Ramkhalawon B, Moore KJ, Cronstein BN. Netrin-1 and its receptor Unc5b are novel targets for the treatment of inflammatory arthritis. *FASEB J* 2016; 30(11): 3835-44.
<http://dx.doi.org/10.1096/fj.201600615R> PMID: 27502509
 - [25] Sun L, Ju T, Wang T, *et al.* Decreased netrin-1 and correlated Th17/Tregs balance disorder in A β (1-42) induced Alzheimer's disease Model Rats. *Front Aging Neurosci* 2019; 11: 124.
<http://dx.doi.org/10.3389/fnagi.2019.00124> PMID: 31191297
 - [26] Bruikman CS, Vreken D, Hoogeveen RM, *et al.* Netrin-1 and the grade of atherosclerosis are inversely correlated in humans. *Arterioscler Thromb Vasc Biol* 2020; 40(2): 462-72.
<http://dx.doi.org/10.1161/ATVBAHA.119.313624> PMID: 31801376
 - [27] Lin Z, Jin J, Bai W, Li J, Shan X. Netrin-1 prevents the attachment of monocytes to endothelial cells via an anti-inflammatory effect. *Mol Immunol* 2018; 103: 166-72.
<http://dx.doi.org/10.1016/j.molimm.2018.08.021> PMID: 30290313
 - [28] Luo Y, Raible D, Raper JA. Collapsin: a protein in brain that induces the collapse and paralysis of neuronal growth cones. *Cell* 1993; 75(2): 217-27.
[http://dx.doi.org/10.1016/0092-8674\(93\)80064-L](http://dx.doi.org/10.1016/0092-8674(93)80064-L) PMID: 8402908
 - [29] Luo Y, Shepherd I, Li J, Renzi MJ, Chang S, Raper JA. A family of molecules related to collapsin in the embryonic chick nervous system. *Neuron* 1995; 14(6): 1131-40.
[http://dx.doi.org/10.1016/0896-6273\(95\)90261-9](http://dx.doi.org/10.1016/0896-6273(95)90261-9) PMID: 7605628
 - [30] Semaphorin Nomenclature Committee. Letter to the editor: Unified nomenclature for the semaphorins/collapsins. *Cell*. 1997; 97: pp. 551-2.
 - [31] Worzfeld T, Offermanns S. Semaphorins and plexins as therapeutic targets. *Nat Rev Drug Discov* 2014; 13(8): 603-21.
<http://dx.doi.org/10.1038/nrd4337> PMID: 25082288
 - [32] Chauvet S, Cohen S, Yoshida Y, *et al.* Gating of Sema3E/-PlexinD1 signaling by neuropilin-1 switches axonal repulsion to attraction during brain development. *Neuron* 2007; 56(5): 807-22.
<http://dx.doi.org/10.1016/j.neuron.2007.10.019> PMID: 18054858
 - [33] Iragavarapu-Charyulu V, Wojcikiewicz E, Urdaneta A. Semaphorins in angiogenesis and autoimmune diseases: therapeutic targets? *Front Immunol* 2020; 11: 346.
<http://dx.doi.org/10.3389/fimmu.2020.00346> PMID: 32210960
 - [34] Franzolin G, Tamagnone L. Semaphorin signaling in cancer-associated inflammation. *Int J Mol Sci* 2019; 20(2): 377.
<http://dx.doi.org/10.3390/ijms20020377> PMID: 30658382
 - [35] Hirai H, Maru Y, Hagiwara K, Nishida I, Takaku F. A novel putative tyrosine kinase receptor encoded by the eph gene. *Science* 1987; 238(4834): 1717-20.
<http://dx.doi.org/10.1126/science.2825356> PMID: 2825356
 - [36] Taylor H, Campbell J, Nobes CD. Ephs and ephrins. *Curr Biol* 2017; 27(3): R90-5.
<http://dx.doi.org/10.1016/j.cub.2017.01.003> PMID: 28171762
 - [37] Pasquale EB. Eph-ephrin bidirectional signaling in physiology and disease. *Cell* 2008; 133(1): 38-52.
<http://dx.doi.org/10.1016/j.cell.2008.03.011> PMID: 18394988
 - [38] Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; 372(6505): 425-32.
<http://dx.doi.org/10.1038/372425a0> PMID: 7984236
 - [39] van der Klaauw AA, Farooqi IS. The hunger genes: pathways to obesity. *Cell* 2015; 161(1): 119-32.
<http://dx.doi.org/10.1016/j.cell.2015.03.008> PMID: 25815990
 - [40] Kaur Y, de Souza RJ, Gibson WT, Meyre D. A systematic review of genetic syndromes with obesity. *Obes Rev* 2017; 18(6): 603-34.

- <http://dx.doi.org/10.1111/obr.12531> PMID: 28346723
- [41] van der Klaauw AA, Croizier S, Mendes de Oliveira E, *et al.* INTERVAL; UK10K Consortium. Human semaphorin 3 variants link melanocortin circuit development and energy balance. *Cell* 2019; 176(4): 729-42.e18.
- [42] <http://dx.doi.org/10.1016/j.cell.2018.12.009> PMID: 30661757
- Zeltser LM. Axon guidance molecules implicated in early-onset obesity. *Trends Neurosci* 2019; 42(7): 439-40.
- [43] <http://dx.doi.org/10.1016/j.tins.2019.03.005> PMID: 30981443
- Wolf Y, Boura-Halfon S, Cortese N, *et al.* Brown-adipose-tissue macrophages control tissue innervation and homeostatic energy expenditure. *Nat Immunol* 2017; 18(6): 665-74.
- [44] <http://dx.doi.org/10.1038/nri.3746> PMID: 28459435
- Hassan M, Latif N, Yacoub M. Adipose tissue: friend or foe? *Nat Rev Cardiol* 2012; 9(12): 689-702.
- [45] <http://dx.doi.org/10.1038/nrcardio.2012.148> PMID: 23149834
- Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. *J Clin Invest* 2011; 121(6): 2094-101.
- [46] <http://dx.doi.org/10.1172/JCI45887> PMID: 21633177
- Mejert N, Wilfling F, Esteve D, *et al.* Semaphorin 3C is a novel adipokine linked to extracellular matrix composition. *Diabetologia* 2013; 56(8): 1792-801.
- [47] <http://dx.doi.org/10.1007/s00125-013-2931-z> PMID: 23666167
- Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. *Obes Rev* 2010; 11(1): 11-8.
- [48] <http://dx.doi.org/10.1111/j.1467-789X.2009.00623.x> PMID: 19656312
- Schipper HS, Prakken B, Kalkhoven E, Boes M. Adipose tissue-resident immune cells: key players in immunometabolism. *Trends Endocrinol Metab* 2012; 23(8): 407-15.
- [49] <http://dx.doi.org/10.1016/j.tem.2012.05.011> PMID: 22795937
- Hersoug LG, Møller P, Loft S. Gut microbiota-derived lipopolysaccharide uptake and trafficking to adipose tissue: implications for inflammation and obesity. *Obes Rev* 2016; 17(4): 297-312.
- [50] <http://dx.doi.org/10.1111/obr.12370> PMID: 26712364
- Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome—an allostatic perspective. *Biochim Biophys Acta* 2010; 1801: 338-49.
- [51] <http://dx.doi.org/10.1016/j.bbalip.2009.12.006>
- Ghaben AL, Scherer PE. Adipogenesis and metabolic health. *Nat Rev Mol Cell Biol* 2019; 20(4): 242-58.
- [52] <http://dx.doi.org/10.1038/s41580-018-0093-z> PMID: 30610207
- Shimizu I, Yoshida Y, Moriya J, *et al.* Semaphorin3E-induced inflammation contributes to insulin resistance in dietary obesity. *Cell Metab* 2013; 18(4): 491-504.
- [53] <http://dx.doi.org/10.1016/j.cmet.2013.09.001> PMID: 24093674
- Sharma M, Schlegel M, Brown EJ, *et al.* Netrin-1 alters adipose tissue macrophage fate and function in obesity. *Immunometabolism* 2019; 1(2): e190010. PMID: 31428465
- [54] Mori T, Maeda N, Inoue K, *et al.* A novel role for adipose ephrin-B1 in inflammatory response. *PLoS One* 2013; 8(10): e76199.
- [55] <http://dx.doi.org/10.1371/journal.pone.0076199> PMID: 24098442
- Övünç Hacıhamdioğlu D, Hacıhamdioğlu B, Altun D, Müftüoğlu T, Karademir F, Süleymanoğlu S. Urinary Netrin-1: A new biomarker for the early diagnosis of renal damage in obese children. *J Clin Res Pediatr Endocrinol* 2016; 8(3): 282-7.
- [56] <http://dx.doi.org/10.4274/jcrpe.2828> PMID: 27087488
- Sanders TR, Kim DW, Glendinning KA, Jasoni CL. Maternal obesity and IL-6 lead to aberrant developmental gene expression and deregulated neurite growth in the fetal arcuate nucleus. *Endocrinology* 2014; 155(7): 2566-77.
- [57] <http://dx.doi.org/10.1210/en.2013-1968> PMID: 24773340
- O'Brien PD, Hinder LM, Callaghan BC, Feldman EL. Neurological consequences of obesity. *Lancet Neurol* 2017; 16(6): 465-77.
- [58] [http://dx.doi.org/10.1016/S1474-4422\(17\)30084-4](http://dx.doi.org/10.1016/S1474-4422(17)30084-4) PMID: 28504110
- Yau PL, Castro MG, Tagani A, Tsui WH, Convit A. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. *Pediatrics* 2012; 130(4): e856-64.
- [59] <http://dx.doi.org/10.1542/peds.2012-0324> PMID: 22945407
- Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Häring HU. Brain insulin resistance at the crossroads of metabolic and cognitive disorders in humans. *Physiol Rev* 2016; 96(4): 1169-209.
- [60] <http://dx.doi.org/10.1152/physrev.00032.2015> PMID: 27489306
- Sharma S, Zhuang Y, Gomez-Pinilla F. High-fat diet transition reduces brain DHA levels associated with altered brain plasticity and behaviour. *Sci Rep* 2012; 2: 431.
- [61] <http://dx.doi.org/10.1038/srep00431> PMID: 22666534
- Molteni R, Barnard RJ, Ying Z, Roberts CK, Gómez-Pinilla F. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience* 2002; 112(4): 803-14.
- [62] [http://dx.doi.org/10.1016/S0306-4522\(02\)00123-9](http://dx.doi.org/10.1016/S0306-4522(02)00123-9) PMID: 12088740
- Molteni R, Wu A, Vaynman S, Ying Z, Barnard RJ, Gómez-Pinilla F. Exercise reverses the harmful effects of consumption of a high-fat diet on synaptic and behavioral plasticity associated to the action of brain-derived neurotrophic factor. *Neuroscience* 2004; 123(2): 429-40.
- [63] <http://dx.doi.org/10.1016/j.neuroscience.2003.09.020> PMID: 14698750
- Valcarcel-Ares MN, Tucsek Z, Kiss T, *et al.* Obesity in Aging exacerbates neuroinflammation, dysregulating synaptic function-related genes and altering eicosanoid synthesis in the mouse hippocampus: potential role in impaired synaptic plasticity and cognitive decline. *J Gerontol A Biol Sci Med Sci* 2019; 74(3): 290-8.
- [64] <http://dx.doi.org/10.1093/gerona/gly127> PMID: 29893815
- Cisternas P, Salazar P, Serrano FG, *et al.* Fructose consumption reduces hippocampal synaptic plasticity underlying cognitive performance. *Biochim Biophys Acta* 2015; 1852(11): 2379-90.
- [65] <http://dx.doi.org/10.1016/j.bbdis.2015.08.016> PMID: 26300486
- Calvo-Ochoa E, Hernández-Ortega K, Ferrera P, Morimoto S, Arias C. Short-term high-fat-and-fructose feeding produces insulin signaling alterations accompanied by neurite and synaptic reduction and astroglial activation in the rat hippocampus. *J Cereb Blood Flow Metab* 2014; 34(6): 1001-8.
- [66] <http://dx.doi.org/10.1038/jcbfm.2014.48> PMID: 24667917
- Anand KS, Dhikav V. Hippocampus in health and disease: An overview. *Ann Indian Acad Neurol* 2012; 15(4): 239-46.
- [67] <http://dx.doi.org/10.4103/0972-2327.104323> PMID: 23349586
- Siegel A, Sapru HN. Essential neuroscience. 2015; Vol. 81.
- [68] Bettio LEB, Thacker JS, Rodgers SP, Brocardo PS, Christie BR, Gil-Mohapel J. Interplay between hormones and exercise on hippocampal plasticity across the lifespan. *Biochim Biophys Acta Mol Basis Dis* 2020; 1866(8): 165821.
- [69] <http://dx.doi.org/10.1016/j.bbdis.2020.165821> PMID: 32376385
- Temido-Ferreira M, Coelho JE, Pousinha PA, Lopes LV. Novel players in the aging synapse: impact on cognition. *J Caffeine Adenosine Res* 2019; 9(3): 104-27.
- [70] <http://dx.doi.org/10.1089/caff.2019.0013> PMID: 31559391
- Booker SA, Vida I. Correction to: Morphological diversity and connectivity of hippocampal interneurons. *Cell Tissue Res* 2019; 376(3): 485-6.
- [71] <http://dx.doi.org/10.1007/s00441-019-03014-w> PMID: 30945003
- Ziemann U, Ilić TV, Pauli C, Meintzschel F, Ruge D. Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *J Neurosci* 2004; 24(7): 1666-72.
- [72] <http://dx.doi.org/10.1523/JNEUROSCI.5016-03.2004> PMID: 14973238
- Dong Z, Bai Y, Wu X, *et al.* Hippocampal long-term depression mediates spatial reversal learning in the Morris water maze. *Neuropharmacology* 2013; 64: 65-73.
- [73] <http://dx.doi.org/10.1016/j.neuropharm.2012.06.027> PMID: 22732443
- Bliss TVP, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 1993; 361(6407): 31-9.
- [74] <http://dx.doi.org/10.1038/361031a0> PMID: 8421494
- Panja D, Bramham CR. BDNF mechanisms in late LTP formation: A synthesis and breakdown. *Neuropharmacology* 2014; 76(Pt C): 664-76.
- <http://dx.doi.org/10.1016/j.neuropharm.2013.06.024> PMID:

- 23831365
- [75] Kuipers SD, Trentani A, Tiron A, Mao X, Kuhl D, Bramham CR. BDNF-induced LTP is associated with rapid Arc/Arg3.1-dependent enhancement in adult hippocampal neurogenesis. *Sci Rep* 2016; 6: 21222.
<http://dx.doi.org/10.1038/srep21222> PMID: 26888068
- [76] Pang PT, Teng HK, Zaitsev E, *et al.* Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. *Science* 2004; 306: 487-91.
<http://dx.doi.org/10.1126/science.1100135>
- [77] Agrawal R, Gomez-Pinilla F. 'Metabolic syndrome' in the brain: deficiency in omega-3 fatty acid exacerbates dysfunctions in insulin receptor signalling and cognition. *J Physiol* 2012; 590(10): 2485-99.
<http://dx.doi.org/10.1113/jphysiol.2012.230078> PMID: 22473784
- [78] Agrawal R, Noble E, Vergnes L, Ying Z, Reue K, Gomez-Pinilla F. Dietary fructose aggravates the pathobiology of traumatic brain injury by influencing energy homeostasis and plasticity. *J Cereb Blood Flow Metab* 2016; 36(5): 941-53.
<http://dx.doi.org/10.1177/0271678X15606719> PMID: 26661172
- [79] Oestreicher AB, De Graan PNE, Gispen WH, Verhaagen J, Schrama LH. B-50, the growth associated protein-43: Modulation of cell morphology and communication in the nervous system. *Prog Neurobiol* 1997; 53(6): 627-86.
- [80] Benowitz LJ, Routtenberg A. GAP-43: an intrinsic determinant of neuronal development and plasticity. *Trends Neurosci* 1997; 20(2): 84-91.
[http://dx.doi.org/10.1016/S0166-2236\(96\)10072-2](http://dx.doi.org/10.1016/S0166-2236(96)10072-2) PMID: 9023877

REVIEW ARTICLE



Pathophysiological Features of Obesity and its Impact on Cognition: Exercise Training as a Non-Pharmacological Approach



Daniela S. Inoue¹, Bárbara M. Antunes¹, Mohammad F.B. Maideen^{2,3} and Fábio S. Lira^{1,*}

¹Exercise and Immunometabolism Research Group, Post-Graduation Program in Movement Sciences, Department of Physical Education, State University (UNESP), School of Technology and Sciences, Presidente Prudente, São Paulo, Brazil; ²Faculty of Health Sciences, Thermal Ergonomics Laboratory, The University of Sydney, NSW, Australia; ³Charles Perkins Centre, The University of Sydney, NSW, Australia

Abstract: Background: The number of individuals with obesity is growing worldwide and this is a worrying trend, as obesity has shown to cause pathophysiological changes, which result in the emergence of comorbidities such as cardiovascular disease, diabetes mellitus type 2 and cancer. In addition, cognitive performance may be compromised by immunometabolic deregulation of obesity. Although in more critical cases, the use of medications is recommended, a physically active lifestyle is one of the main foundations for health maintenance, making physical training an important tool to reduce the harmful effects of excessive fat accumulation.

Aim: The purpose of this review of the literature is to present the impact of immunometabolic alterations on cognitive function in individuals with obesity, and the role of exercise training as a non-pharmacological approach to improve the inflammatory profile, energy metabolism and neuroplasticity in obesity.

Method: An overview of the etiology and pathophysiology of obesity to establish a possible link with cognitive performance in obese individuals, with the executive function being one of the most affected cognitive components. In addition, the brain-derived neurotrophic factor (BDNF) profile and its impact on cognition in obese individuals are discussed. Lastly, studies showing regular resistance and/or aerobic training, which may be able to improve the pathophysiological condition and cognitive performance through the improvement of the inflammatory profile, decreased insulin resistance and higher BDNF production are discussed.

Conclusion: Exercise training is essential for reestablishment and maintenance of health by increasing energy expenditure, insulin resistance reduction, anti-inflammatory proteins and neurotrophin production corroborating to upregulation of body function.

Keywords: Adipose tissue, cognition, neuroinflammation, hormones, physical activity, diabetes mellitus type 2.

1. INTRODUCTION

Obesity has reached epidemic proportions that affect different ethnic, age and socioeconomic groups [1]. A survey conducted by the Global Burden of Disease (GBD) encompassing 195 countries revealed that, in 2015, the obese population doubled in about 70 countries compared to the findings of a similar survey performed in 1980, reflecting more than 603 million adults worldwide [2]. These data raise concerns from the public health perspective, as obesity is a major risk factor for morbidity and mortality. This is because excessive accumulation of body fat, especially in the abdominal region, causes changes in different levels of body's functions, leading to cycles of physiological compensations, which overload body systems generating a pathophysiological condition [3, 4] related to health risk [1]. Thus, adiposity reduction is recommended to improve the health of obese individuals [5].

The term 'obesity' is derived from the Latin word *obesus*, which means devouring or eating away [6]. However, the etiology

of obesity has shown to be much more complex than simply over-eating calories, since this pathophysiological condition ranges from metabolic disorders to cognitive impairments, which can interfere with aspects of behavior, such as self-control, decision-making, attention and memory, making it difficult for the affected individual to adhere to a healthy lifestyle, thus reinforcing the complexity of this condition, with a myriad of factors which maximize the difficulty for a successful treatment [3, 4, 7-9].

There are different approaches to treat pathophysiological responses as a result of obesity, among them being exercise training as a form of a non-pharmacological treatment. The role of exercise is unique for health promotion, as not only does it increase energy expenditure thus providing support to the weight loss process, the body's responses to exercise also seem to benefit other aspects directly related to the pathophysiological condition of obesity, such as anti-inflammatory responses [10].

Thus, this review of the literature aims to present how immunometabolic alterations can impact the cognitive function of obese individuals and the non-pharmacological role of exercise training to improve this pathophysiological condition.

2. OBESITY

2.1. Etiology

The etiology of obesity can be studied from a phylogenetic and/or ontogenetic perspective. From a phylogenetic perspective,

*Address correspondence to this author at the Exercise and Immunometabolism Research Group, Post-Graduation Program in Movement Sciences, Department of Physical Education, State University (UNESP), School of Technology and Sciences, Rua Roberto Simonsen, 305, 19060-900, Presidente Prudente, São Paulo, Brazil; Tel: 55 18 3229-5906; Fax: 55 18 3229-5710; E-mail: fabio.lira@unesp.br

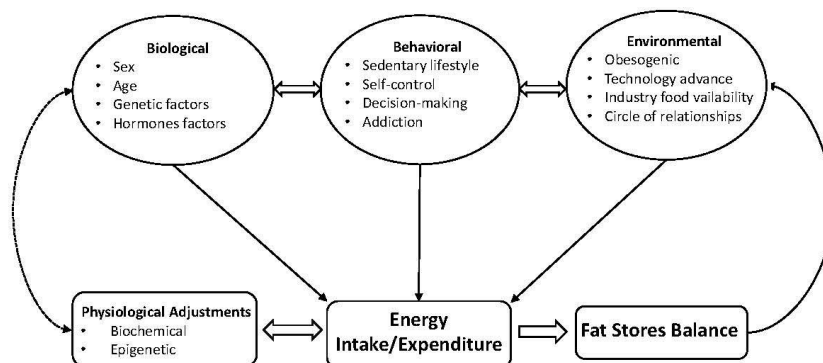


Fig. (1). Ecological model for understanding obesity. Adapted from Egger e Swinburn [7].

the human race seems to inherit evolutionary traits that are predisposed to conserve fat storage as a survival trait [11]. This argument appears justifiable with the notion that our human ancestors would have difficulty in obtaining their food due to its great shortage in early times. Some researchers [11, 12] consider this, the hypothesis of a "Thrifty gene" [12] as one reason, even in small part, to combat obesity. Others, such as Speakman [13], argue that the obesity phenotype is a "Drifty gene". In other words, there would be genetic randomness to its epidemic. From an ontogenetical perspective, there are different types of influences that may or may not corroborate with the establishment of obesity during the developmental process of each individual, being a consequence of the interaction between genetic load and intrinsic and/or extrinsic factors. Egger and Swinburn [7] proposed an ecological model to understand the origin of obesity that encompasses three major influences: environmental, biological and behavioral, as described above in Fig. (1).

Environmental and biological influences undoubtedly impact human behavior, and in obesity, some behavioral variables may be compromised. For *example*, in obese individuals, decision-making ability may be impaired, interfering with impulsivity control, which may contribute to the development of binge eating, addiction to certain types of foods, changes in mood, memory and reasoning as well as maintaining a higher sedentary behavior [14-16]. Moreover, situations or environments that generate great mental stress and anxiety can result in an increased intake of food, which may give rise to eating disorders [16, 17].

This brief explanation about the causes of obesity gives us an overview of multifactorial processes (environmental, biological and behavioral, phylogenetic and ontogenetic) that lead to the emergence of this condition. From a molecular level, there are also several changes taking place that result in abnormal tissue function and behavioral responses. Thus, the following section will discuss in more detail the relation between the degree of obesity and its pathophysiological characteristics.

2.2. Pathophysiology of Obesity

The pathophysiological condition of obesity is directly related to location and accumulation of white adipose tissue, which determines the onset of comorbidities related to obesity. Subcutaneous adipose tissue (SAT) differs greatly from visceral adipose tissue (VAT) [18], and Table 1 presents some of these anatomical and physiological differences.

SAT is present in the most superficial layers of the body with protective metabolic characteristics, since it is less metabolically

active and is responsible for capturing free fatty acids (FFA) and triacylglycerol (TAG) excess from the circulation, as shown in Table 1. Despite being responsible for lipid storage, adipocytes of SAT have a determined capacity, which when exceeded, this tissue begins to lose its protective character and the fat starts to accumulate in other sites unsuitable for storage (known as ectopic fat), such as the liver, skeletal muscle and heart, contributing to the development of comorbidities [18, 19].

On the other hand, VAT is located close to organs, which potentiate its metabolic activity (Table 1). This adipose tissue is more sensitive to catecholamines, since it is capable of expressing a large number of β -adrenergic receptors, responsible for stimulating lipolysis and cortisol action, which is found in high concentrations when an individual is under stress, contributing to higher fat accumulation and differentiation of preadipocyte in this region [18]. The perirenal, pericardial, and intra-abdominal adipose tissues (as described above) are *examples* of VAT, which in abnormal conditions can also impair general functions of the body [19], which will be detailed below.

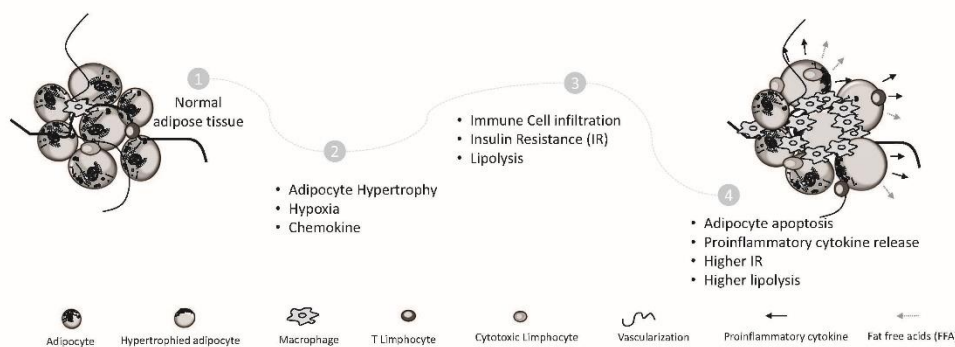
Adipose tissue is a type of connective tissue composed of fat-filled adipocytes that are surrounded by connective tissue matrix, blood vessels, fibroblasts, immune cells and preadipocytes [20]. An important feature of this tissue is its ability to secrete many proteins known as adipokines, cytokines and chemokines, which have autocrine, paracrine and endocrine functions and influence appetite, energy balance, immunity, insulin sensitivity and lipid metabolism, amongst others [18, 19]. Among several adipokines produced by adipose tissue, leptin, adiponectin, tumor necrosis factor- α (TNF- α), interleukin-10 (IL-10), and interleukin-6 (IL-6) will be highlighted here.

Leptin is the major adipokine related to energy balance as it is released proportionally to fat storage. Leptin inhibits orexigenic pathways and activates anorexigenic pathways in the hypothalamus, the part of the brain that is responsible for food intake control and energy expenditure, which allows the maintenance of body mass [21]. Leptin also has the function of angiogenesis, hematopoiesis and immunity. Its main source of production is SAT, although VAT also contributes to blood concentrations [18]. Adiponectin is another protein abundantly produced by adipocytes, especially from VAT [22], and its main function is sensitivity to insulin action that increases glucose uptake and stimulates fatty acid oxidation, whilst inhibiting glycolysis, lipogenesis and gluconeogenesis [23]. In addition, it inhibits the expression of adhesion molecules and stimulates

Table 1. Structural and functional differences in SAT and VAT.

SAT	Characteristics	VAT
The main areas for deposition are gluteofemoral and anterior abdominal wall regions. Covers about 80% of total body fat.	ANATOMICAL DIFFERENCES	Responsible for up to 10 to 20% of total fat in men and 5 to 8% in women. Visceral fat increases with age in both sexes
It is not highly vascularized and venous drainage is done through systemic veins.	VASCULARIZATION	In addition to being highly vascularized due to its anatomical position, venous Blood is drained directly into the liver through the portal vein, providing direct hepatic access to FFA and adipokines secreted by visceral adipocytes
Not highly innervated.	INNERVATION	Highly innervated
Smaller, with higher affinity for capturing FFA and TAG and more sensitive to insulin. Greater capacity for hyperplasia.	ADIPOCYTES	Larger, with higher accumulation of FFA and more resistant to insulin. Greater capacity for hypertrophy
Higher amounts of estrogen receptors, especially in the gluteofemoral region.	RECEPTORS	Higher amounts of glucocorticoid, androgenic and adrenergic receptors
Lower presence.	IMMUNE CELLS	Higher presence and active participation
Lower lipolytic activity.	LIPOLYSIS	Higher lipolytic activity

Adapted from Ibrahim [18]. FFA: Free Fatty Acids; TAG: Triacylglycerol.

**Fig. (2).** Inflammation *via* hypoxia of adipose tissue. Adapted from Virtue and Vidal Puig [31].

IL-10 production, therefore, demonstrating its important anti-atherogenic role [18].

In contrast, TNF- α , IL-10 and IL-6 are mainly produced by immune cells infiltrated into the adipose tissue. TNF- α is the major cytokine produced by macrophages and its function is to regulate biological processes such as differentiation, proliferation and cellular apoptosis, as well as acting on energy metabolism. Simultaneously, lipolysis is increased, which contributes to a higher TAG and FFA blood concentration, as TNF- α impairs the insulin signaling pathway by inhibiting the phosphorylation of insulin receptor substrate 1 (IRS-1) of adipocytes and myocytes [24]. IL-10's function is to prevent an exacerbated inflammatory response by inhibiting proinflammatory cytokine gene transcription, such as TNF- α , and by increasing expression of other anti-inflammatory proteins, such as the receptor of TNF- α [25]. IL-6 plays a role in lipid metabolism by increasing both lipolysis and oxidation of FFA [26].

Excessive lipid accumulation induces adipokines production alteration, making the microenvironment more proinflammatory in an attempt to reestablish the balance of this tissue microenvironment [3, 4, 27, 28]. If these imbalances are not resolved in the long term, this metabolically triggered inflammation may culminate in low-grade chronic inflammation [28].

Chronic positive energy balance increases adiposity, which, to a great extent, impairs blood flow, and as such, some regions of adipose tissue may suffer from hypoxia. This impairment in blood perfusion results in the activation of transcription factors related to endothelial growth and hypoxia, such as hypoxia-inducible factor 1- α (HIF-1 α), which activates the production of chemoattractant proteins and leptin [20, 29]. These factors lead to greater infiltration of different immune cells into adipose tissue and produce more cytokines such as TNF- α and IL-6, which will increase lipolysis as an attempt to reduce adipocyte size and increase oxygen supply. At the same time, a higher release of TNF- α activates adipocyte apoptosis.

tosis attracting more monocytes, lymphocytes and other immune cells within the adipose tissue, potentiating immunometabolic stress (Fig. 2) [27-29].

In addition to adipose tissue hypoxia, endotoxins can trigger inflammatory pathways. High fat intake increases gut permeability, which allows products of Gram-negative bacteria, known as lipopolysaccharides (LPS) to enter the bloodstream and infiltrate body tissues. LPS endotoxin is able to bind to receptors known as Toll-like (TLR), which are abundant in immune cells, triggering pathways related to expression, production and secretion of inflammatory cytokines [30]. Another pathway responsible for chronic low-grade inflammation is related to signaling pathways activated by FFA, particularly saturated fatty acids, which may come from dietary sources, or due to positive inflammation feedback itself [28, 31]. Saturated fatty acids, such as palmitate, seem to incorporate themselves into the plasma membrane, which triggers changes in fluidity while activating proinflammatory signaling [32].

Hypoxia, endotoxemia, and excess of FFA, have common signaling pathways through kinases, which promote gene expression of proinflammatory proteins while inhibiting insulin signaling [28-29]. Among these pathways, the activation of protein kinase C (PKC), c-JUN N-terminal kinase (JNK) and kappa B kinase inhibitor (IKK) culminates with the activation of nuclear factor kappa B (NFkB), responsible for several cytokines gene transcription, including TNF- α and IL-6, and inhibition of the peroxisome proliferator-activated receptor-gamma (PPAR- γ). Thus, since PPAR- γ (which is the transcription factor responsible for the expression of proteins involved in lipid metabolism and insulin sensitivity, such as adiponectin) is inhibited in inflammatory conditions, there is a loss in metabolic energy (both lipid and glycemic) [29].

Thus, with obesity, especially abdominal obesity, proinflammatory pathways are likely to be highly stimulated, resulting in elevated concentrations of TNF- α , IL-6 and leptin, and reduced concentrations of IL-10 and adiponectin leading to local and systemic immunometabolic damage. High concentrations of TNF- α and IL-6 activate lipolysis with increased release of FFA, and when entering the bloodstream, are directed to other tissues, including the liver (*via* portal vein, as mentioned above) [5, 33]. In addition, as described previously, TNF- α inhibits insulin signaling while suppressing adiponectin expression, insulin resistance (IR) may become systemic due to inflammation of adipose tissue [5, 28] (Fig. 3).

IR is the failure of response to insulin in tissues. In obesity, IR seems to function by minimizing adipocyte anabolism in order to avoid further energy storage. However, this condition forces the pancreas to produce a surplus of this hormone, leading to long-term hyperinsulinemia [34, 35]. Several peripheral tissues, such as the liver, adipose and musculoskeletal tissue, depend on insulin for glucose uptake and lipogenesis, however, their responses are impaired due to IR. Thus, hyperinsulinemia may be accompanied by hyperglycemia and hyperlipidemia, increasing the risk of developing other non-transmissible chronic diseases, such as comorbidities of obesity [3, 4], as depicted in Fig. (3).

In addition, metabolic changes in obesity have been associated with impairments in central nervous system (CNS) function (Fig. 3) that may affect behavioral variables, such as cognitive aspects of self-control, cognitive flexibility, working memory and reasoning, as well as being related to the development of psychological disorders, *e.g.* depression and dementia [34].

In summary, the growth of obese population can be recognised by the interaction of its etiological and pathophysiological complexity. The damage which obesity generates in an individual's health has inflammation as one of the causes for IR onset, which in turn, is a risk factor for the development of several obesity-related comorbidities. In this regard, it is thus vital that obese individuals commit to change their behavior patterns in order to preserve their quality of health. However, adherence to lifestyle change is often

low and this fact should not be treated in a simplistic way. This is because functional CNS changes have a strong impact on certain components of cognition that reflect on the individual's behavior, as we will see in the next session.

3. COGNITIVE FUNCTION AND OBESITY

The advancement of science has allowed the expansion of understanding regarding the impact of chronic noncommunicable diseases on the individual. Until a few decades ago, the focus of obesity was centered around diseases such as diabetes, dyslipidemias and cardiovascular diseases. Nowadays, studies have established links between obesity and CNS function, such as cognition [36-39].

Studies have reported the existence of cognitive decline in obese individuals, regardless of age [36, 37, 39], gender [39], presence of psychological diseases [40], socioeconomic factors and cardiovascular diseases [40]. Cognitive changes are related to eating disorders, poor adherence to various types of treatments, addictions [41], impairments in school and professional performance [36], and favoring the development of psychiatric disorders such as mood swings, depression and some types of dementia such as Alzheimer's disease [38].

Understanding what and how the components of cognitive function may be related to obesity is an important tool to aid in the prevention and treatment of this pathophysiological condition.

3.1. Cognitive Function

Cognitive function is the ability to process, integrate, manipulate, store and retrieve information [40] involving different components [42] such as perception [43], attention, [44] learning [45], memory [46] and executive function [47]. The interaction between aspects of cognitive function as well as the performance of each of them influences human behavior. All the functions that make up cognition are interdependent, however, in this review, we will describe executive function.

Executive function is a superior, multidimensional cognitive processes or mental operations used to guide behavior, especially in nonroutine situations, that allow for prediction and action directed toward particular goals. It is also known as self-regulation [47-49] and prioritizing and sequencing information, inhibiting familiar or stereotyped behaviors, creating and maintaining an idea of what task or information is most relevant to current purposes, resisting distracting information or irrelevant tasks, using relevant information to supporting decision-making, categorizing or abstracting common elements between items, and dealing with new information or situations [48]. Executive function is commonly classified into three main domains: inhibition, cognitive flexibility and working memory [39, 41].

Inhibition, also known as inhibitory control or self-control, refers to the ability to suppress automatic and/or impulsive responses [39] able to control attention, behaviors, thoughts and emotions, overriding a strong internal predisposition or external attraction to execute a more appropriate or necessary response [41]. Cognitive flexibility is the ability to shift attention in response to changes in focus or rules, where appropriate [39], *i.e.*, ability to be flexible enough to adjust to priority changes in the face of unexpected opportunity, and being flexible to change opinions or similar situations [41]. Working memory also fits into the executive function, since it has the ability to monitor the relevance of the received stimuli and to relate information in memory as needed [39]. The executive function supports reasoning, creativity, recombination of various elements of thinking, and allows planning and decision making [41].

The relation between working memory and self-control is a two-way path, as one supports the other. For example, for an individual to stay focused on a situation that requires more mental ef-

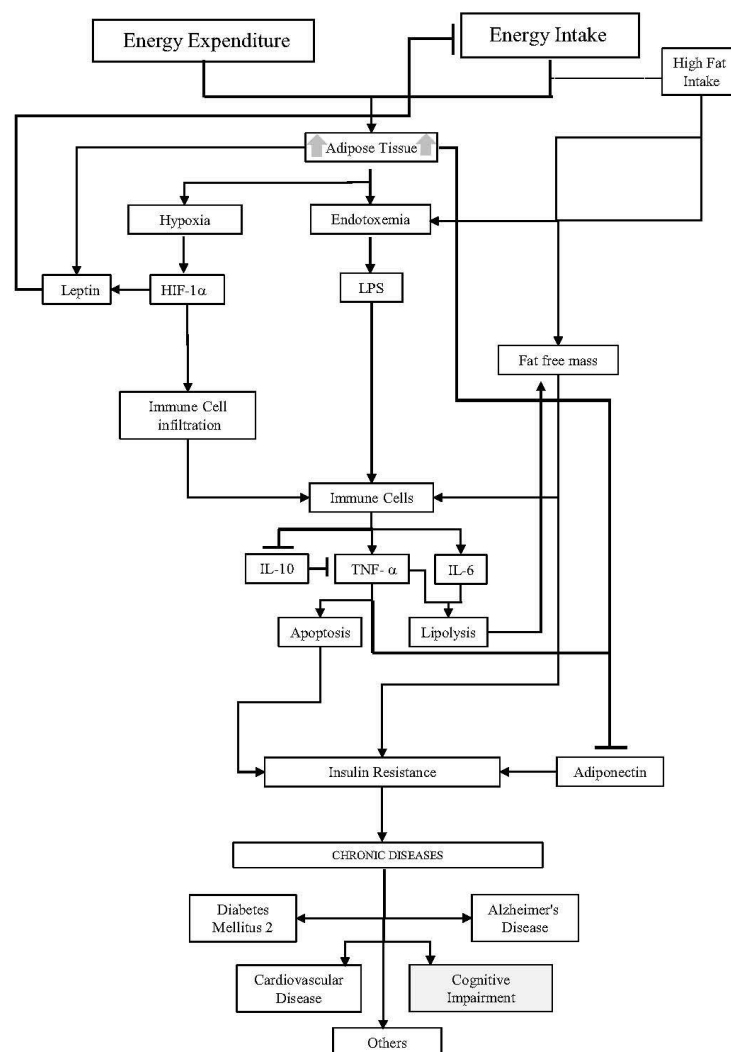


Fig. (3). Pathophysiological condition of obesity.

CHO: Carbohydrate; **LPS:** lipopolysaccharides; **HIF-1α:** Hypoxia-inducible Factor-1α; **TNF-α:** Tumor Necrosis Factor-α; **IL-10:** Interleukin-10; **IL-6:** Interleukin-6.

fort, it is necessary to inhibit any other stimuli to avoid shifting focus, in which case, self-control supports a particular task that uses memories in order for the task to be executed. On the other hand, in a situation where it is necessary to avoid automatic attitudes or to issue standard answers, working memory will support self-control by concentrating on information that should guide behavior, thus reducing the chance of errors. Cognitive flexibility is built on those two domains. This is demonstrated in a situation where we need to change the perspective [39]. For example, in order to change a par-

ticular habit, it will be necessary to activate self-control to "block" routine actions, whilst working memory is triggered to use previous information in order to reinforce attention to implant the new pattern. Therefore, the three domains, although classified differently, operate interconnectedly.

In addition to these three primary domains, decision-making, verbal fluency, and planning make up executive function [39] as well. Decision making is defined as a cognitive and/or emotional process that occurs whenever an individual has to make a choice

between several possibilities based on personal goals and values [14, 39]. Verbal fluency is the ability to generate as many words as possible from a semantic category at a given time [39]. Planning is a formulation, evaluation, and selection of a sequence of thoughts and actions to reach a goal [39]. All cited skills (and many others) make up executive function, which, in turn, is part of cognitive function. Impairments in cognitive processes might impact different aspects of life.

Executive function is the cognitive variable that is more compromised in obese individuals [39, 40] with a performance reduction in this ability and consequently, impacting the behavior of the obese individual. Thus, it is necessary to understand this relationship between the pathophysiological condition of obesity and cognitive performance.

3.2. Cognitive Impairment in Obesity

In the past, researchers believed that adiposity alone did not directly contribute to poor cognitive function, but indirectly through cardiovascular changes that would then impact cognition [40]. However, several studies have recently confirmed a direct relationship between obesity and impairment of cognitive function [37, 38, 40].

Smith *et al.* [40], after a bibliographic survey that included studies with children, adolescents and adults, found that since childhood and adolescence, obese individuals already presented a cognitive deficit in relation to children with normal BMI, and this same relation remained in adulthood. In addition, Smith *et al.* [39] highlighted, although obese individuals have lower motor fitness, language development and memory, the executive function seems to be the most affected component. A recent meta-analysis performed by Yang *et al.* [39] found poorer self-control, working memory, cognitive flexibility, decision-making, planning and verbal fluency performance in human obese individuals when compared with eutrophic pairs. However, the causes of such an association remain uncertain.

In the present review, we sought to elucidate this association through three perspectives: preexistence of cognitive deficit as a risk factor for the development of obesity; common factors (genetics and excessive fat intake) that simultaneously influence the accumulation of visceral fat and cognitive performance; and the pathophysiological condition of obesity as a predictor of impairment in cognition (Fig. 4).

Longitudinal studies have found that better cognitive performance, especially of executive function, adjusted for socioeconomic factors and maternal BMI, were related to a low chance of developing obesity from childhood [50, 51] until adulthood [51]. This is because the functioning of the prefrontal cortex influences energy control ability and food intake impulses along with the hypothalamic and limbic system [50, 52]. Thus, according to the first relationship (Fig. 4A), individuals may become obese due to a limitation of these preexisting neurological functions.

A second perspective suggests the existence of a common factor that leads to increased visceral fat while impairing cognitive

performance at the same time (Fig. 4B). Smith *et al.* [40] stated that these two conditions may share the same common genetic variants, for example in the FTO gene, which is related to the development of obesity and seems to be involved with lower brain volume as well. In addition, excessive lipid consumption can lead to both an acute cognitive deficit while its accumulation in adipose tissue and other body tissues may lead to a chronic cognitive deficit [28, 40]. Edwards *et al.* [53] found that a high-fat diet consumption during a seven-day period reduced reaction time and the attention of sedentary men. Animal studies confirm that FFA crosses the blood-brain barrier (BBB) and triggers activation of proinflammatory signaling pathways, such as those occurring in other tissues, corroborating with an inflamed neuronal environment, also called neuroinflammation [54].

The third perspective (Fig. 4C) considers that the pathophysiological condition of obesity is a strong factor for cognitive decline [40]. Schwartz *et al.* [37], using a sample of 983 adolescents (with a mean BMI of 21.79 kg/m² for boys and 21.91 kg/m² for girls), performed a cross-sectional analysis involving cognitive assessment and abdominal magnetic resonance image, and concluded that visceral fat contributed negatively to executive function of young adolescents. Another study, conducted by Yau *et al.* [36], compared adolescents with and without metabolic syndrome and found those with the pathological condition presented worse in academic and intellectual performance and demonstrated reduced attention, apart from having a reduction in hippocampal volume and a greater amount of cerebrospinal fluid. These findings suggest that immunometabolic imbalances may compromise cognitive function [36-38].

Studies with intravenous and intranasal insulin administration have found the role of insulin as a neuroregulatory peptide [55] in several regions of the brain such as the hypothalamus, which regulates anorexigenic pathways in the frontal cortex, with the function of determining eating behavior [56]. However, obese individuals seem to have lower concentrations of insulin in CNS, since higher values are found in plasma than in the cerebrospinal fluid. This concentration difference is related to the preliminary existence of IR in the BBB, decreasing its passage to CNS. Thus, lower concentrations of insulin add to its resistance to action (due to neuroinflammation), which strongly impairs brain functionality, including cognitive function [38, 56].

In addition to insulin, glucocorticoids, mainly represented by cortisol in humans, also has important effects on brain function. Increased amounts of abdominal fat seem to be associated with greater responsiveness to the hypothalamic-pituitary and adrenal (HPA) axis [57, 58]; therefore, in obesity, this hormone can be found in higher concentrations. Due to its lipophilic characteristics, the cortisol is able to easily cross the BBB as well as the cell membrane and then bind to specific intracellular receptors in the brain. Among the receptor types, we highlight the glucocorticoid receptor (GR) that has a lower affinity with cortisol and, therefore, is usually activated when cortisol is in higher concentrations, as in the case of obesity, and may impair prefrontal cortex performance, impacting executive function. In the hippocampus, the activation of GR by

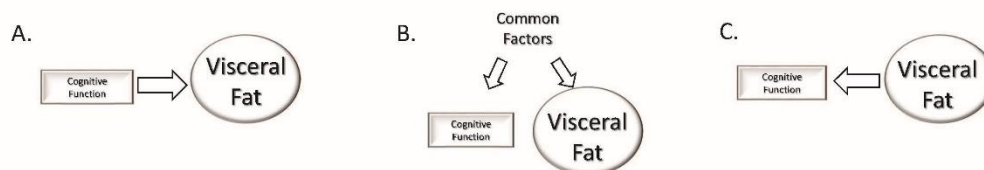


Fig. (4). (A, B, C) Possible relationships between obesity and cognitive deficit.

cortisol seems to suppress long-term potentiation (LTP), an important mechanism for memory consolidation [59].

Although cortisol is recognized for its anti-inflammatory, immunosuppressive and immunomodulatory action, such as the inhibition of proliferation and activation of lymphocyte apoptosis, it has recently been recognized as a precursor of proinflammatory immune responses in the CNS. This was demonstrated in rats, in which stress protocols not only failed to suppress but rather induced TNF- α concentrations in the hippocampus and prefrontal cortex *versus* LPS stimuli. Thus, stress-induced glucocorticoids may have a proinflammatory action in CNS [60].

In addition to glucocorticoids and changes in insulin concentrations and its action, FFA and LPS resulting from a high-fat diet and more permeability through BBB (as a consequence of chronic inflammation of low-grade inflammation present in obesity and allowing more cytokines to cross the BBB as well), contribute to neuroinflammation. Neuroinflammation seems to be a triggering factor for several CNS disorders, which, due to excess of proinflammatory cytokines, impairs neural feedback circuits related to energy balance, to HPA axis control, and to trigger neurodegeneration processes [38, 59].

Thus, the pathophysiological condition of obesity has been linked to a reduction in brain function and structures, including the prefrontal cortex and hippocampus, as immunometabolic alterations may be related to inhibition of neuroplasticity, neurogenesis and neuronal growth processes [38, 59]. In this context, brain-derived neurotrophic factor (BDNF) is a protein that has been prominent in neuronal health, encompassing both cognitive function and aspects of energy metabolism. Thus, in the next topic, we will give a brief exposition about this protein and its relation with the pathophysiology of obesity.

3.3. Brain-derived Neurotrophic Factor

Early research on BDNF arose in 1978 when a group led by Yves-Alain Barde and Hans Thoenen identified a factor produced by glial cells that supported different sensory neuron survival in relation to functional and immunological criteria of other factors already known, such as nerve growth factor (NGF). In 1980, the same group demonstrated that mammalian brains also had a similar survival factor when, in 1982, Barde *et al.* [61] were able to extract 2 μ g of this new factor from 3 kg of pig brain, which they called a neurotrophic factor. Since then, several experiments have been performed with brain-derived neurotrophic factor - BDNF, and confirming its ability to provide neurogenesis, synaptic and axonal remodeling, neuronal differentiation and neuroregeneration [62-64].

BDNF is a member of the neurotrophin family of growth factors, such as NGF, neurotrophin-3 (NT-3), NT4, which are found in mammals and in humans, and is widely present in the hippocampus, amygdala, cerebral cortex and hypothalamus. It is located on chromosome 11p13 and expressed from a single locus composed of 11 exons and nine promoter regions [65]. Studies with rodents have contributed to understanding from synthesis to the function of this neurotrophin. Its transcription is closely regulated by neural activity and is initiated by the activation of α -amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) and N-methyl-D-aspartate (NMDA) propionic acid receptors by the glutamate released from the presynaptic neuron. These receptors allow an influx of sodium and calcium, respectively. Calcium then binds to calmodulin II-dependent protein kinase, which in turn activates transcription factors of the element-binding proteins in response to cAMP (CREB) and NF- κ B inducing transcription of the gene *Bdnf* that is transported into the endoplasmic reticulum [66].

In the endoplasmic reticulum, it is synthesized as a pre-pro-neurotrophin and in the Golgi complex, it is stored in vesicles as a pro-neurotrophin, also called pro-BDNF (~32kDa). Pro-BDNF may or may not undergo the action of intracellular proteases within the

vesicle itself, such as furin (an endopeptidase), and extracellular proteases, such as metalloproteinases (MMP), especially MMP-9, and plasmin, a product dependent of plasminogen cleavage by tissue plasminogen activator (tPA), considered as a critical step to conversion of pro-BDNF to mature BDNF (mBDNF). Pro-BDNF also gives rise to two other isoforms: pro-domain (~28kDa) and mBDNF (~14kDa) [67, 68].

The release of BDNF isoforms is dependent on the activation of Na⁺ (depolarization) channels, especially in high-frequency states (~100 Hz), with a subsequent influx of Ca²⁺ by voltage-dependent Ca²⁺ channels (VDCC) and NMDA and AMPA receptors or release of stored intracellular Ca²⁺ itself [69].

All isoforms are active in the human body, however, they present antagonistic responses by activating two different classes of receptors placed on the plasma membrane. Responses to mBDNF are well-established. On ligation to receptors, the dimerization of tropomyosin-related B kinases (TrkB) is initiated followed by autophosphorylation of tyrosine residues in the intracellular kinase domain. Within seconds to minutes, tyrosine phosphorylation is followed by activation of several signaling cascades, such as phosphatidylinositol-3-kinase (PI3K), mitogen-activated protein kinase (MAPK) and activation of phospholipase-C-signaling pathways (PLC- γ) that are related to survival, dendritic growth and plasticity of nervous system cells [66, 69, 70]. This is because mBDNF increases the release of neurotransmitters and prolongs the opening of ion channels, making synaptic transmission more effective, which favors LTP, for example [69].

The functional importance of pro-domain of the BDNF, or pro-domain, has been demonstrated by the discovery of a single nucleotide polymorphism in which valine (val) 66 is replaced by methionine (met), known as Val66Met. This polymorphism is related to eating and executive function disorders [71], memory deficits and abnormal hippocampal function in humans. In the cell domain, the Val/Met substitution affects the intracellular traffic of the BDNF to the synapses and attenuates BDNF release dependent on the regulated activity, without affecting its constitutive secretion [69]. Research into all possible functions of pro-BDNF is still scarce, limiting the understanding of these pathways. When pro-BDNF binds to its p75 neurotrophin receptor (p75^{NTR}) related to sortilin, it triggers neuronal apoptosis, axon shortening, negatively regulates hippocampal and spinal cord density [72], and under certain long-term conditions, may lead to neurodegeneration. Fig. (5) shows the sketch of mBDNF and pro-BDNF signaling pathways.

Studies have shown low concentrations of BDNF in obese individuals [73, 74]. Kaur *et al.* [75] found a relationship between higher central adiposity, lower BDNF concentration and lower executive function of healthy middle-aged adults. Human studies have found poorer executive function performance and lower frontal cortex thickness [76], which could be associated with changes in BDNF concentrations in obesity, which reinforces evidence of interaction between the pathophysiological conditions of obesity, cognition and BDNF. However, further studies are needed to help understand how this interaction occurs.

3.4. BDNF and Obesity

Research verifying the mechanisms involving obesity, cognition and BDNF is still limited. There is some evidence to show that the immunometabolic imbalances as a response to hypertrophy of adipose tissue could affect concentrations of BDNF.

Human studies have shown an association between cortisol concentrations and BDNF [77, 78]. However, it is in animal studies that such relationships become more elucidated. According to Suri and Vaidya [79], glucocorticoids, when chronically elevated (up to 10 days) and with increased GR activation, seem to act at multiple levels in the regulation of BDNF, ranging from transcriptional control to post-synaptic signaling. At the transcriptional level, gluco-

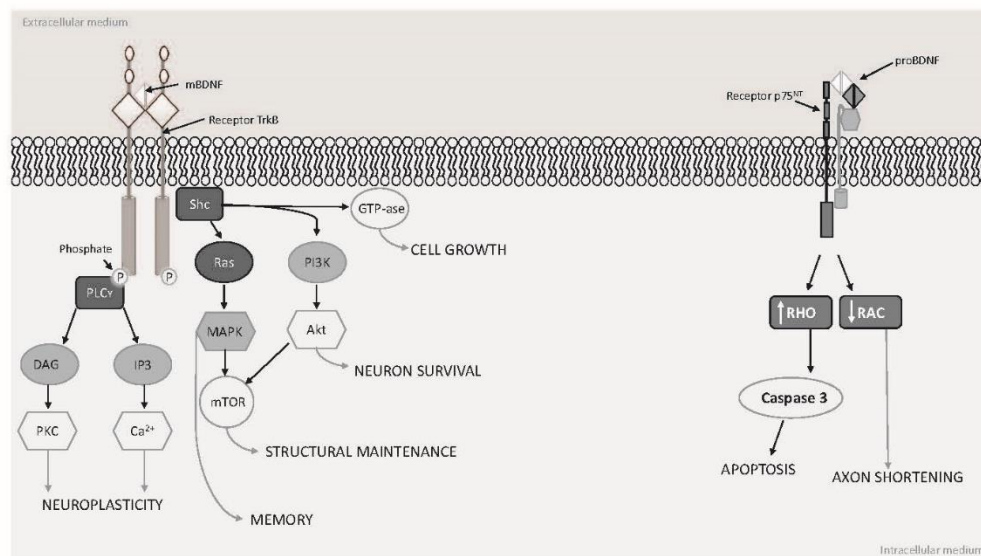


Fig. (5). Exemplification of activation pathways of the mBDNF and pro-BDNF isoforms.

Adapted from Foltran e Diaz [68], Blum e Konnerth [69]; Chao [70]. **Shc** - adaptor protein families Src homology and Collagen; **GTP-ase** - hydrolyze guanosine triphosphate enzymes; **PI3K** - Phosphatidylinositol-3 Kinase; **MAPK** - Mitogen-activated Protein Kinases; **mTOR** - Mammalian Target of Rapamycin; **AKT** - Protein Kinase B; **PLC-γ** - fosforilase gama C; **DAG** - Diacylglycerol to **IP3** - Inositol 1,4,5-trisphosphate to **PKC** - Protein Kinase C, **RHO** - Ras Homologous; **RAC** - Subfamily of the Rho.

corticoids can activate glucocorticoid response elements (GRE) that in turn, interfere with CREB transcriptional activity. Glucocorticoids may also interfere with the activities of furin, tPA and MMP, which may alter the cleavage rate of pro-BDNF and consequently the availability of mBDNF. In addition, glucocorticoids may influence the trafficking of vesicles containing the BDNF isoforms from dendrites to the axon terminals, impairing their release in the synaptic cleft. Finally, glucocorticoids can inhibit mBDNF/TrkB signaling by impairing the activation of MAPK, PLC-γ and PI3K pathways, which may alter neuronal functions. However, studies involving glucocorticoids and pro-BDNF are still limited [79].

In relation to inflammation, the involvement of neurotrophin is complex. Firstly, BDNF plays a role in the maturation and survival of T lymphocytes, especially under stress conditions [80, 81]. Kerscheneister *et al.* [80] showed a bidirectional relationship between the immune system and the nervous system, when they found that immunological cells (CD4⁺, CD8⁺ lymphocytes, B cells and monocytes) were able to produce BDNF and a supernatant of these cells after a 72-hour incubation, which was able to give support in the survival of these sensory neurons. However, these same authors suggested that only nerve cells could be activated by BDNF due to the TrkB receptor subtype (gp145TrkB), while other cells, such as the immunological ones, would carry the truncated TrkB receptor subtype (gp195), which could not activate intracellular signaling. In 2003, Bayas *et al.* [82] tested this hypothesis, by demonstrating that the stimulation of peripheral blood mononuclear cells (PBMC) by recombinant BDNF was able to increase IL-4, IFN-γ and TNF-α mRNA expression among other cytokines, showing that immune cells may also be influenced by BDNF.

Secondly, inflammation can induce the production of BDNF within neurons, immune cells and other organs, leading to increased

bloodstream BDNF concentrations. TNF-α and IL-6 appear to increase BDNF. Huang *et al.* [83] found that LPS-stimulated PBMCs were able to increase BDNF production in young obese adults, suggesting that in inflammatory conditions, immune cells, via increased IL-6, are stimulated to produce neurotrophins in order to minimize neuronal damage associated with obesity, such as cognitive deficit. In addition, Luo *et al.*, [72] showed under conditions of inflammation, the conversion of pro-BDNF into mBDNF seems to be inhibited and higher concentrations of pro-BDNF stimulate infiltration of immune cells culminating in an increase in proinflammatory cytokines. However, these mechanisms still need to be elucidated and whether this occurs in humans and in the condition of low-grade chronic inflammation, it is still unclear. Thus, further studies are needed to understand the relationship of different BDNF isoforms and immunometabolic responses in the obesity condition.

Thirdly, BDNF seems to have an anti-inflammatory effect on neuroinflammation, since intranasal and intracerebral administration in rats increased IL-10 concentrations and decreased TNF-α [81]. However, studies evaluating the anti-inflammatory effect of BDNF and its isoforms in humans are scarce.

In contrast to the energy metabolism, several studies have pointed to a relationship between BDNF concentrations and insulin sensitivity [84-86]. This is because BDNF favors the pathway of glucose uptake and mitochondrial biogenesis, contributing to cellular homeostasis, mainly in the CNS [66, 87]. Currently, a negative correlation has been reported between concentrations of BDNF and fasting glycemia, obesity, and blood TAG concentrations; on the other hand, a positive correlation with high-density lipoprotein HDL-c concentrations [87]. In the cellular environment, BDNF increases the production of neuronal ATP in some pathways: stimulating the expression of the Glucose-3 transporter (GLUT3), via Ca²⁺ influx and activation of calmodulin, regulating the transcrip-

tion of peroxisome proliferator-activated receptor- γ coactivator-1 α (PGC-1 α), thus increasing the number of mitochondria [66]. In addition to inhibiting dietary behavior (appetite suppression), BDNF also influences the metabolism of various peripheral organs, such as skeletal muscle, to improve insulin sensitivity [66].

Thus, it is possible that in the presence of chronic low-grade inflammation, this pathway *via* BDNF/energy metabolism is impaired. Therefore, changes in BDNF concentrations bring immunometabolic damage that may impact the neuronal/cognitive health of obese individuals. In addition, it is important to note that most of the studies with BDNF do not discriminate isoforms, whereas those involving pro-BDNF are scarce.

Although the pathophysiological picture of obesity that may impair cognitive performance presented so far, it is necessary to develop strategies to combat this disease. Although there are pharmaceutical interventions that are available, and that the awareness that the control of food intake is fundamental, the practice of a regular physical activity is one of the main therapeutic tools in the treatment of obesity. Optimizing the "use" of this tool can bring greater health benefits.

4. EXERCISE TRAINING AS A NON-PHARMACOLOGICAL APPROACH

Regular physical exercise is recognized for its multiple health benefits. Physical exercise enhances metabolism and energy expenditure, which corroborates a reduction of fat storage [88-90]; increases cardiorespiratory fitness, favoring oxygen supply, energy substrate and metabolite removal in all body tissues, including CNS [91, 92]; modifies the production, release and action of hormones, especially those related to energy metabolism [10, 91]; modulates inflammatory profile, which is highly activated under pathophysiological conditions [10, 93], and is able to improve cognitive function [94-97].

Application of different types and structures of exercise promotes benefits; however, aerobic training is generally recommended for reducing body fat, although the implementation of resistance training is recommended for increasing and maintaining muscle mass [88], as well as favoring the improvement of energy metabolism [98].

4.1. Physical Training and Chronic Low-grade Inflammation

Since obesity is known to be characterized by a chronic low-grade inflammation that favors the onset and development of other comorbidities, several studies have explored the anti-inflammatory function of physical exercise [10, 99]. This scenario can be guided by three possible mechanisms: intra-abdominal adipose tissue reduction, lower activation of immune cells (*via* TLR-4), and increased anti-inflammatory factors. Reductions in intra-abdominal adipose tissue are related to higher expression of metabolic proteins such as GLUT4 and PGC-1 α , increased mitochondria and lipid oxidation in muscle and adipose tissue [99], which result in higher energy expenditure, even in the absence of total body mass reduction. Once intra-abdominal adipose tissue is reduced, there will be a consequent increase in adiponectin and lower production of TNF- α and IL-6, making this tissue less inflamed and, therefore, less resistant to insulin action [10].

The effects of aerobic training also seem to be related to lower activation of peripheral immune cells. Mechanisms related to this process have yet to be clarified, but it is speculated that these cells will be able to internalize chemokine receptors under the influence of exercise training as a negative feedback response. Physical exercise training also seems to reduce TLR-4 expression in macrophages and consequently decrease T lymphocyte activation (*via* MHC II) and proinflammatory cytokine production. Hormonal (mainly adrenal) oscillations resulting from exercise training favor the reduction of T lymphocyte infiltration in adipose tissue as well in the bloodstream [10].

Concomitantly, exercise training itself is responsible for modulating the production and secretion of hormones, such as adrenal hormones, as well as stimulating the production of signaling factors by muscle contraction, called myokines [10]. Regarding adrenal hormones, both cortisol and adrenaline are increased according to exercise intensity. In this condition, there are acute elevations of cortisol that exert an anti-inflammatory effect by inhibiting immune cells, while adrenaline inhibits proinflammatory TLR-4 pathways [10]. These hormones act in conjunction with the release of IL-6 by muscle contraction during exercise. IL-6 released as myokine is related to energy storage (glycogen) and anti-inflammatory effects (by a subsequent IL-10 and IL-1ra releasing). The magnitude of IL-6 secretion depends on intensity and exercise duration, apart from the physical fitness level of the individual [10, 100]. These anti-inflammatory mechanisms from exercise training lead to a reduction in IR and, as stated earlier in this review, IR is a triggering factor for many comorbidities associated with obesity, including its relation to cognitive impairments.

4.2. Exercise Training, Cognitive Function and BDNF

Taking into account the different protocols of physical exercise, mainly resistance and aerobic (high-intensity or moderate-intensity performed at continuous or intermittent form) training, several studies have shown their effects on speed and cognition accuracy [101], information processing in CNS [102], neurocognitive performance [103], BDNF regulation [104, 105] and myokines production, which is related to improvement in cognitive function as FNDC5, irisin and cathepsin B increase [100].

In addition to modulations imposed by different protocols of exercise training, it is important to highlight metabolic status (presence or absence of illness) as well as the individual's physical fitness condition as determining factors for targeting the magnitude of response associated with physical exercise. In this line, Edwards and Loprinzi [106] evidenced that high physical fitness and low sedentary behavior were jointly associated with the highest cognitive function in older adults (60-85 years), suggesting that maximizing cardiorespiratory fitness and reducing sedentary behavior may be the most optimal stimulus for enhancing cognitive function.

Recently, Engeroff *et al.* [107] demonstrated that in healthy older adults (>65 years), they reported a beneficial association between regular practice of physical activity and brain metabolism, given that the ATP concentration in the brain is positively associated with habitual physical activity. This suggests that higher ATP concentrations may indicate a greater neuronal energy reserve in physically active participants and, in addition, BDNF analysis revealed a beneficial association with habitual physical activity whereas sedentary behavior was negatively associated with BDNF. More recently, the same group evidenced the association of lifelong physical activity with cognitive function and brain health by correlating between the mean energy expenditure of leisure physical activity from a lifespan perspective, with cognitive function, mainly attention, and brain plasticity, as seen by N-acetylaspartate to choline ratios [108].

Besides brain function and metabolism, some studies have reported morphological adaptation imposed by physical exercise in cerebral structure by an increase in brain volume and/or mass, especially by neurogenesis at hippocampus area [109-112]. An interesting review suggested that at least 80% of the total grey matter volume is modifiable by physical activity [113]. In a study conducted by Ruscheweyh *et al.* [114], a positive association was observed between physical activity and local gray matter volume, memory score and a trend to BDNF increase, without differences between exercise intensity groups, suggesting that beneficial effects of physical activity on memory function occur independently of its intensity, possibly mediated by local grey matter volume and some neurotrophic biomarkers. Together, these findings lead us to hypothesize that limiting the time spent in sedentary behavior and to

Table 2. Effects of acute and chronic exercise on aspects related to cognitive function, neurotrophins and brain health.

References	Sample	Sample Age	Exercise Protocol	Results
Suzuki <i>et al.</i> [127]	Older adults with mild cognitive impairment (n=100)	>65 years	Compared a multicomponent exercise (90 min/d, 2 d/wk, 40 times) versus education control group after 6 months of intervention.	Better Mini-Mental State Examination and logical memory scores, ↓ whole brain cortical atrophy in the exercised group.
Baker <i>et al.</i> [117]	Glucose intolerant adults (n=28)	57-83 years	Compared aerobic exercise (4 d/wk for 45–60 min/session performed at 75–85% of HR reserve) versus stretching (control group performing at or below 50% HR reserve) after 6 months of intervention.	Improvement in the executive function (<i>Trails B</i> , Task Switching and interference trials of the <i>Stroop</i>), cardiorespiratory fitness and insulin sensitivity in the aerobic group.
Vaughan <i>et al.</i> [128]	Women without cognitive impairment (n=49)	65-75 years	Compared multimodal class (twice each week during 60-min/session which included cardiovascular, strength and motor fitness training) versus control group after 16 weeks of intervention.	Better neurocognitive performance, balancing ability, mobility, lower extremity function, falls risk and exercise capacity. ↑BDNF.
Kimhy <i>et al.</i> [136]	Individuals with schizophrenia (n=33)	18-55 years	Compared aerobic exercise (utilizing active-play video games and traditional equipments (treadmill, stationary bike and elliptical machine) at 60-75% HR _{max}) versus standard psychiatric treatment after 12 weeks of intervention.	Improvement in the neurocognition (indexed by MATRICS Consensus Cognitive Battery). ↑BDNF.
Ozkul <i>et al.</i> [129]	Patients with multiple sclerosis (n=36)	18-60 years	Compared combined exercise training (aerobic training in treadmill during 30 min 60-80% HR _{max} following by 15 min pilates performed 3 d/wk) versus control group after 8 weeks of intervention.	↑BDNF ↑Functional exercise capacity. ↓Fatigue Improvement in the postural stability.
Walsh <i>et al.</i> [139]	Adolescents with Obesity (n=202)	14-18 years	Compared aerobic and/or resistance training (4d/week in low-intensity, low-volume resistance, and aerobic training) after 4 weeks of intervention.	↑BDNF ↑HOMA-B
Goldfiel <i>et al.</i> [123]	Adolescents with overweight or obesity (n=78)	14-18 years	Compared aerobic training (45min at 65-85% HR _{max}), resistance training (45min 2-3 sets of 8-12 repetitions) and combined training (90min of both protocols) after 4 weeks (4d/week) of intervention.	No changes on serum BDNF.
Goekint <i>et al.</i> [118]	Untrained subjects (n=32)	18-30 years	Compared subjects of strength training program (3 d/week with 3 sets of 10 repetitions at 50-80% RM) versus control subjects after 10 weeks of intervention.	No changes on BDNF, IGF-1, IGFBP-3 and Cognitive assessment.
Ruiz <i>et al.</i> [121]	Women Nonagenarians (n=40)	>90 years	Compared exercised group (3d/week with 2–3 sets of 8-10 repetitions at 30-70% RM) versus control after 8 weeks of interventions.	No changes on ACE, sAPP, BDNF, EGF and <i>TNF-α</i> .
Jørgensen <i>et al.</i> [125]	Patients with multiple sclerosis (n=30)	18-60 years	Compared high intensity resistance training (2 sessions/week with 3-5 sets, 6-10 repetitions at 6-15 RM) versus control after 24 weeks of intervention.	No changes on acute or chronic circulating levels of BDNF.
Hvid <i>et al.</i> [122]	Mobility-limited older adults (n=47)	>75 years	Compared power training (2 sessions/week with 3 sets with 8-10 repetitions at 70-80% RM) versus control group after 12 weeks of intervention.	No changes in the mature and/or total BDNF.
Forti <i>et al.</i> [120]	Older adults (n=40)	62–72 years	Compared progressive strength training (3sets with 10 repetitions progressively increased by 10 % of 1RM every two sessions from 50 up to 70-80 % of 1RM) versus matched control group after 12 weeks of intervention.	No significant change in BDNF.

Table 2 contd...

References	Sample	Sample Age	Exercise Protocol	Results
Tsai <i>et al.</i> [124]	Older adults with amnesic mild cognitive impairment (n=66)	60-80 years	Compared aerobic exercise (30-min bout at 65-75% of HR reserve), strength exercise (30-min bout at 75% of 1RM) and non-exercise intervention (control).	Aerobic exercise: $\uparrow$ BDNF, $\uparrow$ IGF-1 and trend to increase VEGF. Strength exercise: $\uparrow$ IGF-1.
Lee <i>et al.</i> [134]	Healthy teens (n=91)	14-18 years	Compared trained group (training on rowing, swimming, running (>1000m) or triathlon for at least two months prior to the study) <i>versus</i> matched control.	Better frontal and temporal functioning of the brain regions and the levels of BDNF and VEGF interacted with exercise status in predicting frontal and temporal lobe function.
Tonoli <i>et al.</i> [137]	Patients with type 1 diabetes (n=10)	18-44 years	Compared acute high-intensity exercise bout (10 intervals of 60s at 90% of their maximal wattage) <i>versus</i> matched controls.	$\uparrow$ BDNF $\uparrow$ IGF-1 Better performance at congruent and incongruent parts of the Stroop test.
Briken <i>et al.</i> [138]	Patients with multiple sclerosis (n=42)	40-60 years	Compared acute (incremental test until exhaustion) <i>versus</i> chronic (9 weeks) effects of endurance exercise training (2-3 sessions/week at bicycle ergometer).	$\uparrow$ BDNF only after exercise (acute).
Domínguez-Sánchez <i>et al.</i> [130]	Physically Inactive Overweight Adults (n=51)	18-30 years	Compared high-intensity exercise (4 × 4 min intervals at 85-95% HR _{max} interspersed with 4 min of recovery at 75-85% HR _{max}), resistance training (12-15 repetitions per set, at 50-70% RM with 60 s of recovery) and combined high-intensity and resistance exercise.	Resistance training: $\uparrow$ neurotrophin-3 and neurotrophin 4/5. Combined training: $\uparrow$ BDNF and $\uparrow$ neurotrophin-3.

HR - Heart Rate; HR_{max} - Maximal Heart Rate; RM - Maximal Repetition; BDNF - Brain-derived Neurotrophic Factor; HOMA-B - Homeostatic Model Assessment of B-cell Function; IGF-1 - Insulin-like Growth Factor-1; IGFBP-3 - Insulin-like Growth Factor-binding Protein 3; ACE - Angiotensin Converting Enzyme; sAPP - Soluble Amyloid Precursor Protein- α ; EGF - Epidermal Growth Factor; TNF- α - Tumor Necrosis Factor- α ; VEGF - Vascular Endothelial Growth Factor.

maximize physical exercise training performance might benefit not only cardiometabolic but also cognitive health *via* modulated brain metabolism and morphology.

Thus, considering regular exercise training, individuals with higher physical fitness status have lower brain tissue losses, especially in frontal, parietal, and temporal cortex [115], higher brain perfusion and responsiveness of blood vessel [116], and greater neurotrophins production [104, 117]. These adaptations are some of the hypotheses considered to explain the positive impact of physical fitness status in brain health improvement, providing a plausible biological mechanism to explain the benefits of exercise training. Furthermore, varying the modalities and intensity of exercise training seem to be key factors in cognitive modulations imposed by physical exercise.

When investigating the impact of physical exercise on cognitive functions and adaptations, a greater responsiveness to aerobic exercise was observed in the literature and less is known about resistance exercise, postulated by some authors as an efficient protocol. In several human groups (*i.e.* untrained population, obese, women, older adults with or without cognitive impairment), studies did not verify alterations on both BDNF concentrations and cognitive function after acute or long-term resistance training [117-125].

However, it is important to note that some recent studies using isolated resistance/strength exercise identified positive modulation on BDNF concentration [126] although findings are more pronounced when combined with other exercise protocols that give an "aerobic" feature to the training program [127-130]. In this line, a recent study conducted by Domínguez-Sánchez *et al.* [130] with physically inactive overweight adults compared the acute effects of different training protocols (aerobic high-intensity exercise, resistance training and aerobic high-intensity combined with resistance

exercise) and identified that resistance training-only protocols were able to increase neurotrophins 3 and 4/5 whereas combined training altered similar neurotrophins that parallel BDNF. These data regarding resistance exercise led us to consider the training specificity and its periodization, given that when associated with other exercises, mainly aerobic, they seem to promote beneficial effects. In addition, Lira *et al.* [131] hypothesized that the volume of training performed by targeted larger muscles in resistance training has a larger influence on BDNF than overall volume.

As opposed to resistance/strength training, acute or chronic aerobic exercise is widely proposed as an efficient protocol to impose positive modulations on cognitive function and BDNF concentrations in healthy and at-risk populations. A recent study conducted by Antunes *et al.* [132] observed that BDNF concentrations increased after acute aerobic sessions, mainly with high-intensity exercise; however, when looking at physical fitness levels, subjects with lower physical fitness levels had greater increases in BDNF. This finding is similar to a previous study by Babaei *et al.* [133].

Interestingly, the research by Babaei *et al.* [133] also verified significant BDNF increases after acute aerobic and anaerobic sessions but from a long-term perspective, the authors suggest a metabolic adaptation imposed by aerobic exercise training given that the trained group (who are used to competing at domestic championships for more than 10 years) showed a significantly lower basal serum BDNF, when compared with control group (sedentary individuals), and better cognitive function represented by the Pictures Recall memory test. A beneficial chronic adaptation was also suggested by Lee *et al.* [134] when comparing regular exercisers (training on rowing, swimming, running (>1000m) or triathlon for at least two months) and non-exercisers, as the researchers observed a better frontal and temporal functioning of the brain region in the trained group versus the non-trained group. In addition, BDNF and

VEGF concentrations interacted with exercise status in predicting frontal and temporal lobe function, suggesting that beneficial effects are region-specific and are associated with the serum levels of neurotrophic factors.

Overall, it can be inferred that aerobic exercise is capable of modulating cognitive functions, BDNF production or both. With cognitive function, significant adaptations are identified mainly after chronic interventions in different populations, such as improvement in measures of cognitive control and working memory [135] executive function (Trails B, Task Switching and interference trials of Stroop) [117] and neurocognition components such as social cognition, visual learning, verbal fluency, information processing speed and a better ability to attend, concentrate, think flexibly and resist distraction [128, 136].

Unlike cognitive aspects, neurotrophins and other metabolic parameters associated with cognitive improvement show a significant change after an aerobic exercise bout in healthy and at-risk populations. Tonoli *et al.* [137] found that after an acute high-intensity exercise session (10 intervals of 60s at 90% of their maximal wattage), higher BDNF and IGF-1 concentrations were reported; Briken *et al.* [138] identified higher BDNF production only in response to acute exercise testing without pronounced differences after long-term endurance exercise training; and Tsai *et al.* [124] observed significantly greater serum levels of BDNF and IGF-1 and a trend to increase serum levels of VEGF after an acute bout of aerobic exercise (30-min bout at 65-75% of HR reserve). These findings strengthen not only the short-term effects of aerobic exercise on neurotrophin production associated with neurogenesis, neuroplasticity and neuroprotection but also on key molecules responsible for angiogenesis processes and metabolic health.

Table 2 summarizes the outcomes from studies according to different modalities, frequency and intensity of exercise training on aspects related to cognitive function, neurotrophins and brain health.

Based on these studies, the regular practice of physical exercise by the obesity population must be considered to alleviate pathophysiological conditions as exercise training is related to immunometabolic benefits, on top of contributing to BDNF concentrations, thus increasing better cognition performance and weight loss.

CONCLUSION

Given the worldwide epidemic situation of obesity which has transcended the history of humanity, developing strategies to combat this pathological condition is vital. Cognition impairments and obesity are linked by immunometabolic changes, including BDNF levels. Thus, improving insulin signaling and anti-inflammatory profile favoring neurotrophin production are a key pathway to ameliorate body function. Although the use of medication in some cases is recommended to improve metabolic dysfunction present in obesity, regular physical exercise practice is essential to support the re-establishment and maintenance of health by increasing energy expenditure, reducing insulin resistance, anti-inflammatory proteins and neurotrophin production corroborating to upregulation of body metabolism and decreasing consequences of comorbidities. Therefore, exercise training is a powerful non-pharmacological approach against the harmful effects of obesity.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

The study was funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001, and to Fundação de Amparo à Pesquisa do Estado de São Paulo, Brasil (FAPESP) (2015/22402-9; 2016/16712-8; 2017/03947-0) for their support.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] World Health Organization. Obesity. Available at: <https://www.who.int/topics/obesity/en/>
- [2] Afshin A, Forouzanfar MH, Reitsma MB, *et al.* GBD 2015 obesity collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017; 377(1): 13-27. <http://dx.doi.org/10.1056/NEJMoa1614362> PMID: 28604169
- [3] Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. *N Engl J Med* 2017; 376(3): 254-66. <http://dx.doi.org/10.1056/NEJMra1514009> PMID: 28099824
- [4] Gadde KM, Martin CK, Berthoud HR, Heymsfield SB. Obesity: pathophysiology and management. *J Am Coll Cardiol* 2018; 71(1): 69-84. <http://dx.doi.org/10.1016/j.jacc.2017.11.011> PMID: 29301630
- [5] Jensen MD, Ryan DH, Apovian CM, *et al.* American college of cardiology/american heart association task force on practice guidelines; obesity society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the american college of cardiology/american heart association task force on practice guidelines and the obesity society. *J Am Coll Cardiol* 2014; 63(25 Pt B): 2985-3023. <http://dx.doi.org/10.1016/j.jacc.2013.11.004> PMID: 24239920
- [6] Sharma AM, Kushner RF. A proposed clinical staging system for obesity. *Int J Obes* 2009; 33(3): 289-95. <http://dx.doi.org/10.1038/ijo.2009.2> PMID: 19188927
- [7] Egger G, Swinburn B. An "ecological" approach to the obesity pandemic. *BMJ* 1997; 315(7106): 477-80. <http://dx.doi.org/10.1136/bmj.315.7106.477> PMID: 9284671
- [8] Luppino FS, de Wit LM, Bouvy PF, *et al.* Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry* 2010; 67(3): 220-9. <http://dx.doi.org/10.1001/archgenpsychiatry.2010.2> PMID: 20194822
- [9] Locke AE, Kahali B, Berndt SI, *et al.* LifeLines cohort study; ADIPOGen consortium; AGEN-BMI working group; CARDIOGRAM-plusC4D consortium; CKDGen consortium; GLGC; ICBP; MAGIC investigators; MiTHER consortium; MIGen consortium; PAGE consortium; ReproGen consortium; GENIE consortium; international endogene consortium. Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015; 518(7538): 197-206. <http://dx.doi.org/10.1038/nature14177> PMID: 25673413
- [10] Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol* 2011; 11(9): 607-15. <http://dx.doi.org/10.1038/nri3041> PMID: 21818123
- [11] Schwartz MW, Seeley RJ, Zeltser LM, *et al.* Obesity pathogenesis: an endocrine society scientific statement. *Endocr Rev* 2017; 38(4): 267-96. <http://dx.doi.org/10.1210/er.2017-00111> PMID: 28898979
- [12] Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet* 1962; 14: 353-62. PMID: 13937884
- [13] Speakman JR. Thrifty genes for obesity, an attractive but flawed idea, and an alternative perspective: the 'thrifty gene' hypothesis. *Int J Obes* 2008; 32(11): 1611-7. <http://dx.doi.org/10.1038/ijo.2008.161> PMID: 18852699
- [14] Rotge JY, Poitou C, Fossati P, Aron-Wisniewsky J, Oppert JM. Decision-making in obesity without eating disorders: a systematic review and meta-analysis of Iowa gambling task performances. *Obes Rev* 2017; 18(8): 936-42. <http://dx.doi.org/10.1111/obr.12549> PMID: 28429468
- [15] de Rezende LF, Rodrigues Lopes M, Rey-López JP, Matsudo VK, Luiz Odo C. Sedentary behavior and health outcomes: an overview of systematic reviews. *PLoS One* 2014; 9(8): e105620. <http://dx.doi.org/10.1371/journal.pone.0105620> PMID: 25144686

- [16] Wurtman J, Wurtman R. The trajectory from mood to obesity. *Curr Obes Rep* 2018; 7(1): 1-5.
http://dx.doi.org/10.1007/s13679-017-0291-6 PMID: 29218451
- [17] Razzoli M, Pearson C, Crow S, Bartolomucci A. Stress, overeating, and obesity: insights from human studies and preclinical models. *Neurosci Biobehav Rev* 2017; 76(Pt. A): 154-62.
http://dx.doi.org/10.1016/j.neubiorev.2017.01.026 PMID: 28292531
- [18] Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. *Obes Rev* 2010; 11(1): 11-8.
http://dx.doi.org/10.1111/j.1467-789X.2009.00623.x PMID: 19656312
- [19] González-Muniesa P, Martínez-González MA, Hu FB, *et al.* Obesity. *Nat Rev Dis Primers* 2017; 3: 17034.
http://dx.doi.org/10.1038/nrdp.2017.34 PMID: 28617414
- [20] Trayhurn P. Hypoxia and adipose tissue function and dysfunction in obesity. *Physiol Rev* 2013; 93(1): 1-21.
http://dx.doi.org/10.1152/physrev.00017.2012 PMID: 23303904
- [21] Rosen ED, Spiegelman BM. Adipocytes as regulators of energy balance and glucose homeostasis. *Nature* 2006; 444(7121): 847-53.
http://dx.doi.org/10.1038/nature05483 PMID: 17167472
- [22] Motoshima H, Wu X, Sinha MK, *et al.* Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. *J Clin Endocrinol Metab* 2002; 87(12): 5662-7.
http://dx.doi.org/10.1210/jc.2002-020635 PMID: 12466369
- [23] Bouassida A, Chamari K, Zaouali M, Feki Y, Zbidi A, Tabka Z. Review on leptin and adiponectin responses and adaptations to acute and chronic exercise. *Br J Sports Med* 2010; 44(9): 620-30.
http://dx.doi.org/10.1136/bjsm.2008.046151 PMID: 18927166
- [24] Nakamura K, Fuster JJ, Walsh K. Adipokines: a link between obesity and cardiovascular disease. *J Cardiol* 2014; 63(4): 250-9.
http://dx.doi.org/10.1016/j.jcc.2013.11.006 PMID: 24355497
- [25] Cabral-Santos C, de Lima EA Junior, Fernandes IMDC, *et al.* Interleukin-10 responses from acute exercise in healthy subjects: a systematic review. *J Cell Physiol* 2018; 7.
PMID: 30536945
- [26] Xu Y, Zhang Y, Ye J. IL-6: a potential role in cardiac metabolic homeostasis. *Int J Mol Sci* 2018; 19(9): E2474.
http://dx.doi.org/10.3390/ijms19092474 PMID: 30134607
- [27] Grant RW, Dixit VD. Adipose tissue as an immunological organ. *Obesity (Silver Spring)* 2015; 23(3): 512-8.
http://dx.doi.org/10.1002/oby.21003 PMID: 25612251
- [28] Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. *Nature* 2017; 542(7640): 177-85.
http://dx.doi.org/10.1038/nature21363 PMID: 28179656
- [29] Ye J. Emerging role of adipose tissue hypoxia in obesity and insulin resistance. *Int J Obes* 2009; 33(1): 54-66.
http://dx.doi.org/10.1038/ijo.2008.229 PMID: 19050672
- [30] Hersoug LG, Møller P, Loft S. Gut microbiota-derived lipopolysaccharide uptake and trafficking to adipose tissue: implications for inflammation and obesity. *Obes Rev* 2016; 17(4): 297-312.
http://dx.doi.org/10.1111/obr.12370 PMID: 26712364
- [31] Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome-an allostatic perspective. *Biochim Biophys Acta* 2010; 1801(3): 338-49.
http://dx.doi.org/10.1016/j.bbalip.2009.12.006 PMID: 20056169
- [32] Holzer RG, Park EJ, Li N, *et al.* Saturated fatty acids induce c-Src clustering within membrane subdomains, leading to JNK activation. *Cell* 2011; 147(1): 173-84.
http://dx.doi.org/10.1016/j.cell.2011.08.034 PMID: 21962514
- [33] Pessayre D, Mansouri A, Fromenty B. Nonalcoholic steatosis and steatohepatitis. V. Mitochondrial dysfunction in steatohepatitis. *Am J Physiol Gastrointest Liver Physiol* 2002; 282(2): G193-9.
http://dx.doi.org/10.1152/ajpgi.00426.2001 PMID: 11804839
- [34] Williamson R, McNeilly A, Sutherland C. Insulin resistance in the brain: an old-age or new-age problem? *Biochem Pharmacol* 2012; 84(6): 737-45.
http://dx.doi.org/10.1016/j.bcp.2012.05.007 PMID: 22634336
- [35] Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. *Nat Rev Endocrinol* 2017; 13(11): 633-43.
http://dx.doi.org/10.1038/nrendo.2017.90 PMID: 28799554
- [36] Yau PL, Castro MG, Tagani A, Tsui WH, Convit A. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. *Pediatrics* 2012; 130(4): e856-64.
http://dx.doi.org/10.1542/peds.2012-0324 PMID: 22945407
- [37] Schwartz DH, Leonard G, Perron M, *et al.* Visceral fat is associated with lower executive functioning in adolescents. *Int J Obes* 2013; 37(10): 1336-43.
http://dx.doi.org/10.1038/ijo.2013.104 PMID: 23797144
- [38] O'Brien PD, Hinder LM, Callaghan BC, Feldman EL. Neurological consequences of obesity. *Lancet Neurol* 2017; 16(6): 465-77.
http://dx.doi.org/10.1016/S1474-4422(17)30084-4 PMID: 28504110
- [39] Yang Y, Shields GS, Guo C, Liu Y. Executive function performance in obesity and overweight individuals: a meta-analysis and review. *Neurosci Biobehav Rev* 2018; 84: 225-44.
http://dx.doi.org/10.1016/j.neubiorev.2017.11.020 PMID: 29203421
- [40] Smith E, Hay P, Campbell L, Trollor JN. A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obes Rev* 2011; 12(9): 740-55.
http://dx.doi.org/10.1111/j.1467-789X.2011.00920.x PMID: 21991597
- [41] Diamond A. Executive functions. *Annu Rev Psychol* 2013; 64: 135-68.
http://dx.doi.org/10.1146/annurev-psych-113011-143750 PMID: 23020641
- [42] Koziol LF, Budding DE, Chidekel D. From movement to thought: executive function, embodied cognition, and the cerebellum. *Cerebellum* 2012; 11(2): 505-25.
http://dx.doi.org/10.1007/s12311-011-0321-y PMID: 22068584
- [43] Bertoldi ALS, Ladewig I, Israel VL. Influence of selectivity of attention on the development of body awareness in children with motor deficiencies. *Rev Bras Fisioter* 2007; 11: 319-24.
- [44] Ladewig I. A importância da atenção na aprendizagem de habilidades motoras. *Revista Paulista De Educação Física* 2017; (Suppl. 3): 62-71.
http://dx.doi.org/10.11606/issn.2594-5904_rpf.2000.139614
- [45] Bassett DS, Mattar MG. A network neuroscience of human learning: potential to inform quantitative theories of brain and behavior. *Trends Cogn Sci (Regul Ed)* 2017; 21(4): 250-64.
http://dx.doi.org/10.1016/j.tics.2017.01.010 PMID: 28259554
- [46] Mourao CA Junior, Faria NC. Memória. *Psicol Reflex Crit* 2015; 28: 780-8.
- [47] Leung RC, Vogan VM, Powell TL, Anagnostou E, Taylor MJ. The role of executive functions in social impairment in autism spectrum disorder. *Child Neuropsychol* 2016; 22(3): 336-44.
http://dx.doi.org/10.1080/09297049.2015.1005066 PMID: 25731979
- [48] Banich MT. Executive function: the search for an integrated account. *Curr Dir Psychol Sci* 2009; 18: 89-94.
http://dx.doi.org/10.1111/j.1467-8721.2009.01615.x
- [49] Shields GS, Moons WG, Slavich GM. Inflammation, self-regulation, and health: an immunologic model of self-regulatory failure. *Perspect Psychol Sci* 2017; 12(4): 588-612.
http://dx.doi.org/10.1177/1745691616689091 PMID: 28679069
- [50] Guxens M, Mendez MA, Julvez J, *et al.* Cognitive function and overweight in preschool children. *Am J Epidemiol* 2009; 170(4): 438-46.
http://dx.doi.org/10.1093/aje/kwp140 PMID: 19546150
- [51] Osika W, Montgomery SM. Longitudinal birth cohort study. Physical control and coordination in childhood and adult obesity: longitudinal birth cohort study. *BMJ* 2008; 337: a699.
http://dx.doi.org/10.1136/bmj.a699 PMID: 18698093
- [52] Vainik U, Dagher A, Dubé L, Fellows LK. Neurobehavioural correlates of body mass index and eating behaviours in adults: a systematic review. *Neurosci Biobehav Rev* 2013; 37(3): 279-99.
http://dx.doi.org/10.1016/j.neubiorev.2012.11.008 PMID: 23261403
- [53] Edwards LM, Murray AJ, Holloway CJ, *et al.* Short-term consumption of a high-fat diet impairs whole-body efficiency and cognitive function in sedentary men. *FASEB J* 2011; 25(3): 1088-96.
http://dx.doi.org/10.1096/fj.10-171983 PMID: 21106937
- [54] Morris MJ, Beilharz JE, Maniam J, Reichelt AC, Westbrook RF. Why is obesity such a problem in the 21st century? The intersection of palatable food, cues and reward pathways, stress, and cognition. *Neurosci Biobehav* 2014; 58:1-10.
- [55] Gray SM, Meijer RJ, Barrett EJ. Insulin regulates brain function, but how does it get there? *Diabetes* 2014; 63(12): 3992-7.
http://dx.doi.org/10.2337/db14-0340 PMID: 25414013

- [56] Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Häring HU. Brain insulin resistance at the crossroads of metabolic and cognitive disorders in humans. *Physiol Rev* 2016; 96(4): 1169-209. <http://dx.doi.org/10.1152/physrev.00032.2015> PMID: 27489306
- [57] Incollingo Rodríguez AC, Epel ES, White ML, Standen EC, Seckl JR, Tomiyama AJ. Hypothalamic-pituitary-adrenal axis dysregulation and cortisol activity in obesity: a systematic review. *Psychoneuroendocrinology* 2015; 62: 301-18. <http://dx.doi.org/10.1016/j.psyneuen.2015.08.014> PMID: 26356039
- [58] Urwyler SA, Schuetz P, Ebrahimi F, Donath MY, Christ-Crain M. Interleukin-1 antagonism decreases cortisol levels in obese individuals. *J Clin Endocrinol Metab* 2017; 102(5): 1712-8. <http://dx.doi.org/10.1210/je.2016-3931> PMID: 28324042
- [59] Ouane S, Popp J. High Cortisol and the risk of dementia and Alzheimer's disease: a review of the literature. *Front Aging Neurosci* 2019; 11: 43. <http://dx.doi.org/10.3389/fnagi.2019.00043> PMID: 30881301
- [60] García-Buena B, Caso JR, Leza JC. Stress as a neuroinflammatory condition in brain: damaging and protective mechanisms. *Neurosci Biobehav Rev* 2008; 32(6): 1136-51. <http://dx.doi.org/10.1016/j.neubiorev.2008.04.001> PMID: 18468686
- [61] Barde YA, Edgar D, Thoenen H. Purification of a new neurotrophic factor from mammalian brain. *EMBO J* 1982; 1(5): 549-53. <http://dx.doi.org/10.1002/j.1460-2075.1982.tb01207.x> PMID: 7188352
- [62] Lindsay RM, Thoenen H, Barde YA. Placode and neural crest-derived sensory neurons are responsive at early developmental stages to brain-derived neurotrophic factor. *Dev Biol* 1985; 112(2): 319-28. [http://dx.doi.org/10.1016/0012-1606\(85\)90402-6](http://dx.doi.org/10.1016/0012-1606(85)90402-6) PMID: 4076545
- [63] Davies AM, Thoenen H, Barde YA. The response of chick sensory neurons to brain-derived neurotrophic factor. *J Neurosci* 1986; 6(7): 1897-904. <http://dx.doi.org/10.1523/JNEUROSCI.06-07-01897.1986> PMID: 3525775
- [64] Kalcheim C, Barde YA, Thoenen H, Le Douarin NM. *In vivo* effect of brain-derived neurotrophic factor on the survival of developing dorsal root ganglion cells. *EMBO J* 1987; 6(10): 2871-3. <http://dx.doi.org/10.1002/j.1460-2075.1987.tb02589.x> PMID: 3691474
- [65] Pruunsild P, Kazantseva A, Aid T, Palm K, Timmusk T. Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. *Genomics* 2007; 90(3): 397-406. <http://dx.doi.org/10.1016/j.ygeno.2007.05.004> PMID: 17629449
- [66] Marosi K, Mattson MP. BDNF mediates adaptive brain and body responses to energetic challenges. *Trends Endocrinol Metab* 2014; 25(2): 89-98. <http://dx.doi.org/10.1016/j.tem.2013.10.006> PMID: 24361004
- [67] Riffault B, Medina I, Dumon C, et al. Pro-brain-derived neurotrophic factor inhibits GABAergic neurotransmission by activating endocytosis and repression of GABAA receptors. *J Neurosci* 2014; 34(40): 13516-34. <http://dx.doi.org/10.1523/JNEUROSCI.2069-14.2014> PMID: 25274828
- [68] Foltran RB, Diaz SL. BDNF isoforms: a round trip ticket between neurogenesis and serotonin? *J Neurochem* 2016; 138(2): 204-21. <http://dx.doi.org/10.1111/jnc.13658> PMID: 27167299
- [69] Blum R, Konnerth A. Neurotrophin-mediated rapid signaling in the central nervous system: mechanisms and functions. *Physiology (Bethesda)* 2005; 20: 70-8. <http://dx.doi.org/10.1152/physiol.00042.2004> PMID: 15653842
- [70] Chao MV. Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nat Rev Neurosci* 2003; 4(4): 299-309. <http://dx.doi.org/10.1038/nrn1078> PMID: 12671646
- [71] Gratacòs M, González JR, Mercader JM, de Cid R, Urretavizcaya M, Estivill X. Brain-derived neurotrophic factor Val66Met and psychiatric disorders: meta-analysis of case-control studies confirm association to substance-related disorders, eating disorders, and schizophrenia. *Biol Psychiatry* 2007; 61(7): 911-22. <http://dx.doi.org/10.1016/j.biopsych.2006.08.025> PMID: 17217930
- [72] Luo C, Zhong XL, Zhou FH, et al. Peripheral brain derived neurotrophic factor precursor regulates pain as an inflammatory mediator. *Sci Rep* 2016; 6: 27171. <http://dx.doi.org/10.1038/srep27171> PMID: 27251195
- [73] Krabbe KS, Nielsen AR, Krogh-Madsen R, et al. Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. *Diabetologia* 2007; 50(2): 431-8. <http://dx.doi.org/10.1007/s00125-006-0537-4> PMID: 17151862
- [74] Lee SS, Yoo JH, Kang S, et al. The effects of 12 weeks regular aerobic exercise on brain-derived neurotrophic factor and inflammatory factors in juvenile obesity and type 2 diabetes mellitus. *J Phys Ther Sci* 2014; 26(8): 1199-204. <http://dx.doi.org/10.1589/jpts.26.1199> PMID: 25202180
- [75] Kaur S, Gonzales MM, Tarumi T, et al. Serum brain-derived neurotrophic factor mediates the relationship between abdominal adiposity and executive function in middle age. *J Int Neuropsychol Soc* 2016; 22(5): 493-500. <http://dx.doi.org/10.1017/S1355617716000230> PMID: 27026196
- [76] Marqués-Iturria I, Garolera M, Pueyo R, et al. The interaction effect between BDNF val66met polymorphism and obesity on executive functions and frontal structure. *Am J Med Genet B Neuropsychiatr Genet* 2014; 165B(3): 245-53. <http://dx.doi.org/10.1002/ajmg.b.32229> PMID: 24619555
- [77] Begliumini S, Lenzi E, Ninni F, et al. Plasma brain-derived neurotrophic factor daily variations in men: correlation with cortisol circadian rhythm. *J Endocrinol* 2008; 197(2): 429-35. <http://dx.doi.org/10.1677/JOE-07-0376> PMID: 18434373
- [78] Cattaneo A, Cattane N, Begni V, Pariante CM, Riva MA. The human BDNF gene: peripheral gene expression and protein levels as biomarkers for psychiatric disorders. *Transl Psychiatry* 2016; 6(11): e958. <http://dx.doi.org/10.1038/tp.2016.214> PMID: 27874848
- [79] Suri D, Vaidya VA. Glucocorticoid regulation of brain-derived neurotrophic factor: relevance to hippocampal structural and functional plasticity. *Neuroscience* 2013; 239: 196-213. <http://dx.doi.org/10.1016/j.neuroscience.2012.08.065> PMID: 22967840
- [80] Kerschensteiner M, Gallmeier E, Behrens L, et al. Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor *in vitro* and in inflammatory brain lesions: a neuroprotective role of inflammation? *J Exp Med* 1999; 189(5): 865-70. <http://dx.doi.org/10.1084/jem.189.5.865> PMID: 10049950
- [81] Papathanassoglou ED, Miliatidou P, Karanikola MN. May BDNF be implicated in the exercise-mediated regulation of inflammation? Critical review and synthesis of evidence. *Biol Res Nurs* 2015; 17(5): 521-39. <http://dx.doi.org/10.1177/1099800414555411> PMID: 25358684
- [82] Bayas A, Kruse N, Morabadi NF, et al. Modulation of cytokine mRNA expression by brain-derived neurotrophic factor and nerve growth factor in human immune cells. *Neurosci Lett* 2003; 335(3): 155-8. [http://dx.doi.org/10.1016/S0304-3940\(02\)01152-7](http://dx.doi.org/10.1016/S0304-3940(02)01152-7)
- [83] Huang CJ, Mari DC, Whitehurst M, Slusher A, Wilson A, Shibata Y. Brain-derived neurotrophic factor expression *ex vivo* in obesity. *Physiol Behav* 2014; 123(123): 76-9. <http://dx.doi.org/10.1016/j.physbeh.2013.10.004> PMID: 24140987
- [84] Duan W, Guo Z, Jiang H, Ware M, Mattson MP. Reversal of behavioral and metabolic abnormalities, and insulin resistance syndrome, by dietary restriction in mice deficient in brain-derived neurotrophic factor. *Endocrinology* 2003; 144(6): 2446-53. <http://dx.doi.org/10.1210/en.2002-0113> PMID: 12746306
- [85] van der Heide LP, Ramakers GM, Smidt MP. Insulin signaling in the central nervous system: learning to survive. *Prog Neurobiol* 2006; 79(4): 205-21. <http://dx.doi.org/10.1016/j.pneurobio.2006.06.003> PMID: 16916571
- [86] Motamed S, Karimi I, Jafari F. The interrelationship of metabolic syndrome and neurodegenerative diseases with focus on brain-derived neurotrophic factor (BDNF): Kill two birds with one stone. *Metab Brain Dis* 2017; 32(3): 651-65. <http://dx.doi.org/10.1007/s11011-017-9997-0> PMID: 28361262
- [87] Damirchi A, Tehrani BS, Alamdari KA, Babaei P. Influence of aerobic training and detraining on serum BDNF, insulin resistance, and metabolic risk factors in middle-aged men diagnosed with metabolic syndrome. *Clin J Sport Med* 2014; 24(6): 513-8. <http://dx.doi.org/10.1097/JSM.0000000000000082> PMID: 24662570
- [88] Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK. American college of sports medicine. American college of sports medicine position stand. Appropriate physical activity inter-

- vention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc* 2009; 41(2): 459-71.
<http://dx.doi.org/10.1249/MSS.0b013e3181949333> PMID: 19127177
- [89] Keating SE, Johnson NA, Mielke GL, Coombes JS. A systematic review and meta-analysis of interval training *versus* moderate-intensity continuous training on body adiposity. *Obes Rev* 2017; 18(8): 943-64.
<http://dx.doi.org/10.1111/obr.12536> PMID: 28513103
- [90] Wevege M, van den Berg R, Ward RE, Keech A. The effects of high-intensity interval training *vs.* moderate-intensity continuous training on body composition in overweight and obese adults: a systematic review and meta-analysis. *Obes Rev* 2017; 18(6): 635-46.
<http://dx.doi.org/10.1111/obr.12532> PMID: 28401638
- [91] Batacan RB Jr, Duncan MJ, Dalbo VJ, Tucker PS, Fenning AS. Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. *Br J Sports Med* 2017; 51(6): 494-503.
<http://dx.doi.org/10.1136/bjsports-2015-095841> PMID: 27797726
- [92] Rogmo Ø, Moholdt T, Bakken H, *et al.* Cardiovascular risk of high- *versus* moderate-intensity aerobic exercise in coronary heart disease patients. *Circulation* 2012; 126(12): 1436-40.
<http://dx.doi.org/10.1161/CIRCULATIONAHA.112.123117> PMID: 22879367
- [93] Robinson E, Durrer C, Simtchouk S, *et al.* Short-term high-intensity interval and moderate-intensity continuous training reduce leukocyte TLR4 in inactive adults at elevated risk of type 2 diabetes. *J Appl Physiol* 2015; 119(5): 508-16.
<http://dx.doi.org/10.1152/jappphysiol.00334.2015> PMID: 26139217
- [94] Drigny J, Gremeaux V, Dupuy O, *et al.* Effect of interval training on cognitive functioning and cerebral oxygenation in obese patients: a pilot study. *J Rehabil Med* 2014; 46(10): 1050-4.
<http://dx.doi.org/10.2340/16501977-1905> PMID: 25297458
- [95] Enette L, Vogel T, Fanon JL, Lang PO. Effect of interval and continuous aerobic training on basal serum and plasma brain-derived neurotrophic factor values in seniors: a systematic review of intervention studies. *Rejuvenation Res* 2017; 20(6): 473-83.
<http://dx.doi.org/10.1089/rej.2016.1886> PMID: 28498065
- [96] Griffin EW, Mullally S, Foley C, Warmington SA, O'Mara SM, Kelly AM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol Behav* 2011; 104(5): 934-41.
<http://dx.doi.org/10.1016/j.physbeh.2011.06.005> PMID: 21722657
- [97] Knaepen K, Goekint M, Heyman EM, Meeusen R. Neuroplasticity - exercise-induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. *Sports Med* 2010; 40(9): 765-801.
<http://dx.doi.org/10.2165/11534530-000000000-00000> PMID: 20726622
- [98] Inoue DS, De Mello MT, Foschini D, *et al.* Linear and undulating periodized strength plus aerobic training promote similar benefits and lead to improvement of insulin resistance on obese adolescents. *J Diabetes Complications* 2015; 29(2): 258-64.
<http://dx.doi.org/10.1016/j.jdiacomp.2014.11.002> PMID: 25441178
- [99] Stanford KI, Middelbeek RJ, Goodyear LJ. Exercise effects on white adipose tissue: beiging and metabolic adaptations. *Diabetes* 2015; 64(7): 2361-8.
<http://dx.doi.org/10.2337/db15-0227> PMID: 26050668
- [100] Pedersen BK. Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. *Eur J Clin Invest* 2017; 47(8): 600-11.
<http://dx.doi.org/10.1111/eci.12781> PMID: 28722106
- [101] McMorris T, Hale BJ. Differential effects of differing intensities of acute exercise on speed and accuracy of cognition: a meta-analytical investigation. *Brain Cogn* 2012; 80(3): 338-51.
<http://dx.doi.org/10.1016/j.bandc.2012.09.001> PMID: 23064033
- [102] Kamijo K, Nishihira Y, Hatta A, *et al.* Differential influences of exercise intensity on information processing in the central nervous system. *Eur J Appl Physiol* 2004; 92(3): 305-11.
<http://dx.doi.org/10.1007/s00421-004-1097-2> PMID: 15083372
- [103] Olson RL, Chang YK, Brush CJ, Kwok AN, Gordon VX, Alderman BL. Neurophysiological and behavioral correlates of cognitive control during low and moderate intensity exercise. *Neuroimage* 2016; 131: 171-80.
<http://dx.doi.org/10.1016/j.neuroimage.2015.10.011> PMID: 26458515
- [104] Walsh JJ, Edgett BA, Tschakovsky ME, *et al.* Fasting and exercise differentially regulate BDNF mRNA expression in human skeletal muscle applied physiology, nutrition, and metabolism physiologie appliquee. *Nutrition Et Metabolism* 2015; 40: 96-8.
<http://dx.doi.org/10.1139/apnm-2014-0290>
- [105] Santos CC, Diniz TA, Inoue DS, *et al.* Influence to high-intensity intermittent and moderate-intensity continuous exercise on indices of cardio-inflammatory health in men. *J Exerc Rehabil* 2016; 12(6): 618-23.
<http://dx.doi.org/10.12965/jer.1632780.390> PMID: 28119886
- [106] Edwards MK, Loprinzi PD. Combined associations of sedentary behavior and cardiorespiratory fitness on cognitive function among older adults. *Int J Cardiol* 2017; 229: 71-4.
<http://dx.doi.org/10.1016/j.ijcard.2016.11.264> PMID: 27884563
- [107] Engeroff T, Füzéki E, Vogt L, *et al.* Is objectively assessed sedentary behavior, physical activity and cardiorespiratory fitness linked to brain plasticity outcomes in old age? *Neuroscience* 2018; 388: 384-92.
<http://dx.doi.org/10.1016/j.neuroscience.2018.07.050> PMID: 30077618
- [108] Engeroff T, Vogt L, Fleckenstein J, *et al.* Lifespan leisure physical activity profile, brain plasticity and cognitive function in old age. *Aging Ment Health* 2019; 23(7): 811-8.
<http://dx.doi.org/10.1080/13607863.2017.1421615> PMID: 29293024
- [109] Colcombe SJ, Erickson KI, Scalf PE, *et al.* Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci* 2006; 61(11): 1166-70.
<http://dx.doi.org/10.1093/gerona/61.11.1166> PMID: 17167157
- [110] Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci* 2007; 30(9): 464-72.
<http://dx.doi.org/10.1016/j.tins.2007.06.011> PMID: 17765329
- [111] Kobil T, Liu QR, Gandhi K, Mughal M, Shaham Y, van Praag H. Running is the neurogenic and neurotrophic stimulus in environmental enrichment. *Learn Mem* 2011; 18(9): 605-9.
<http://dx.doi.org/10.1101/lm.228301> PMID: 21878528
- [112] Mattson MP. Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. *Cell Metab* 2012; 16(6): 706-22.
<http://dx.doi.org/10.1016/j.cmet.2012.08.012> PMID: 23168220
- [113] Batouli SAH, Saba V. At least eighty percent of brain grey matter is modifiable by physical activity: a review study. *Behav Brain Res* 2017; 332: 204-17.
<http://dx.doi.org/10.1016/j.bbr.2017.06.002> PMID: 28600001
- [114] Ruscheweyh R, Willemer C, Krüger K, *et al.* Physical activity and memory functions: an interventional study. *Neurobiol Aging* 2011; 32(7): 1304-19.
<http://dx.doi.org/10.1016/j.neurobiolaging.2009.08.001> PMID: 19716631
- [115] Colcombe SJ, Erickson KI, Raz N, *et al.* Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol A Biol Sci Med Sci* 2003; 58(2): 176-80.
<http://dx.doi.org/10.1093/gerona/58.2.M176> PMID: 12586857
- [116] Davenport MH, Hogan DB, Eskes GA, Longman RS, Poulin MJ. Cerebrovascular reserve: the link between fitness and cognitive function? *Exerc Sport Sci Rev* 2012; 40(3): 153-8.
<http://dx.doi.org/10.1097/JES.0b013e3182553430> PMID: 22504726
- [117] Baker LD, Frank LL, Foster-Schubert K, *et al.* Aerobic exercise improves cognition for older adults with glucose intolerance, a risk factor for Alzheimer's disease. *J Alzheimers Dis* 2010; 22(2): 569-79.
<http://dx.doi.org/10.3233/JAD-2010-100768> PMID: 20847403
- [118] Goekint M, De Pauw K, Roelands B, *et al.* Strength training does not influence serum brain-derived neurotrophic factor. *Eur J Appl Physiol* 2010; 110(2): 285-93.
<http://dx.doi.org/10.1007/s00421-010-1461-3> PMID: 20467874
- [119] Correia PR, Pansani A, Machado F, *et al.* Acute strength exercise and the involvement of small or large muscle mass on plasma brain-derived neurotrophic factor levels. *Clinics (São Paulo)* 2010; 65(11): 1123-6.
<http://dx.doi.org/10.1590/S1807-59322010001100012> PMID: 21243284

- [120] Forti LN, Njemini R, Beyer L, *et al.* Strength training reduces circulating interleukin-6 but not brain-derived neurotrophic factor in community-dwelling elderly individuals. *Age (Dordr)* 2014; 36(5): 9704.
<http://dx.doi.org/10.1007/s11357-014-9704-6> PMID: 25128203
- [121] Ruiz JR, Gil-Bea F, Bustamante-Ara N, *et al.* Resistance training does not have an effect on cognition or related serum biomarkers in nonagenarians: a randomized controlled trial. *Int J Sports Med* 2015; 36(1): 54-60.
PMID: 25329433
- [122] Hvid LG, Nielsen MKF, Simonsen C, Andersen M, Caserotti P. Brain-derived neurotrophic factor (BDNF) serum basal levels is not affected by power training in mobility-limited older adults - A randomized controlled trial. *Exp Gerontol* 2017; 93: 29-35.
<http://dx.doi.org/10.1016/j.exger.2017.03.019> PMID: 28392271
- [123] Goldfield GS, Kenny GP, Prud'homme D, *et al.* Effects of aerobic training, resistance training, or both on brain-derived neurotrophic factor in adolescents with obesity: the hearty randomized controlled trial. *Physiol Behav* 2018; 191: 138-45.
<http://dx.doi.org/10.1016/j.physbeh.2018.04.026> PMID: 29679660
- [124] Tsai CL, Ukropce J, Ukropcová B, Pai MC. An acute bout of aerobic or strength exercise specifically modifies circulating exerkine levels and neurocognitive functions in elderly individuals with mild cognitive impairment. *Neuroimage Clin* 2017; 17: 272-84.
<http://dx.doi.org/10.1016/j.nicl.2017.10.028> PMID: 29527475
- [125] Jørgensen MLK, Kjølhede T, Dalgas U, Hvid LG. Plasma brain-derived neurotrophic factor (BDNF) and sphingosine-1-phosphat (S1P) are NOT the main mediators of neuroprotection induced by resistance training in persons with multiple sclerosis-a randomized controlled trial. *Mult Scler Relat Disord* 2019; 31: 106-11.
<http://dx.doi.org/10.1016/j.msard.2019.03.029> PMID: 30965275
- [126] Church DD, Hoffman JR, Mangine GT, *et al.* Comparison of high-intensity vs. high-volume resistance training on the BDNF response to exercise. *J Appl Physiol* 2016; 121(1): 123-8.
<http://dx.doi.org/10.1152/japplphysiol.00233.2016> PMID: 27231312
- [127] Suzuki T, Shimada H, Makizako H, *et al.* A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. *PLoS One* 2013; 8(4): e61483.
<http://dx.doi.org/10.1371/journal.pone.0061483> PMID: 23585901
- [128] Vaughan S, Wallis M, Polit D, Steele M, Shum D, Morris N. The effects of multimodal exercise on cognitive and physical functioning and brain-derived neurotrophic factor in older women: a randomised controlled trial. *Age Ageing* 2014; 43(5): 623-9.
<http://dx.doi.org/10.1093/ageing/afu010> PMID: 24554791
- [129] Ozkul C, Gucu-Gunduz A, Irkec C, *et al.* Effect of combined exercise training on serum brain-derived neurotrophic factor, suppressors of cytokine signaling 1 and 3 in patients with multiple sclerosis. *J Neuroimmunol* 2018; 316: 121-9.
<http://dx.doi.org/10.1016/j.jneuroim.2018.01.002> PMID: 29329698
- [130] Domínguez-Sánchez MA, Bustos-Cruz RH, Velasco-Orjuela GP, *et al.* Acute effects of high intensity, resistance, or combined protocol on the increase of level of neurotrophic factors in physically inactive overweight adults: the brainfit study. *Front Physiol* 2018; 9: 741.
<http://dx.doi.org/10.3389/fphys.2018.00741> PMID: 29997519
- [131] Lira FS, Conrado de Freitas M, Gerosa-Neto J, Cholewa JM, Rossi FE. Comparison between full-body vs. split-body resistance exercise on the brain-derived neurotrophic factor and immunometabolic response. *J Strength Cond Res* 2018. In press.
<http://dx.doi.org/10.1519/JSC.0000000000002653> PMID: 30395543
- [132] Antunes BM, Rossi FE, Teixeira AM, Lira FS. Short-time high-intensity exercise increases peripheral BDNF in a physical fitness-dependent way in healthy men. *Eur J Sport Sci* 2019; 4: 1-8.
<http://dx.doi.org/10.1080/17461391.2019.1611929> PMID: 31057094
- [133] Babaei P, Damirchi A, Mehdipoor M, Tehrani BS. Long term habitual exercise is associated with lower resting level of serum BDNF. *Neurosci Lett* 2014; 566: 304-8.
<http://dx.doi.org/10.1016/j.neulet.2014.02.011> PMID: 24572590
- [134] Lee TM, Wong ML, Lau BW, Lee JC, Yau SY, So KF. Aerobic exercise interacts with neurotrophic factors to predict cognitive functioning in adolescents. *Psychoneuroendocrinology* 2014; 39: 214-24.
<http://dx.doi.org/10.1016/j.psychneuen.2013.09.019> PMID: 24149089
- [135] Moreau D, Kirk IJ, Waldie KE. High-intensity training enhances executive function in children in a randomized, placebo-controlled trial. *eLife* 2017; 6: e25062.
<http://dx.doi.org/10.7554/eLife.25062> PMID: 28825973
- [136] Kimhy D, Vakhrusheva J, Bartels MN, *et al.* The impact of aerobic exercise on brain-derived neurotrophic factor and neurocognition in individuals with schizophrenia: a single-blind, randomized clinical trial. *Schizophr Bull* 2015; 41(4): 859-68.
<http://dx.doi.org/10.1093/schbul/sbv022> PMID: 25805886
- [137] Tonoli C, Heyman E, Roelands B, *et al.* BDNF, IGF-I, glucose and insulin during continuous and interval exercise in type 1 diabetes. *Int J Sports Med* 2015; 36(12): 955-9.
<http://dx.doi.org/10.1055/s-0035-1548886> PMID: 26212245
- [138] Briken S, Rosenkranz SC, Keminer O, *et al.* Effects of exercise on Irisin, BDNF and IL-6 serum levels in patients with progressive multiple sclerosis. *J Neuroimmunol* 2016; 299: 53-8.
<http://dx.doi.org/10.1016/j.jneuroim.2016.08.007> PMID: 27725121
- [139] Walsh JJ, D'Angiulli A, Cameron JD, *et al.* Changes in the brain-derived neurotrophic factor are associated with improvements in diabetes risk factors after exercise training in adolescents with obesity: the HEARTY randomized controlled trial. *Neural Plast* 2018; 2018: 7169583.
<http://dx.doi.org/10.1155/2018/7169583> PMID: 30363954