

**The Effect of Diet and Exercise Interventions for
the Treatment of Male Obesity Induced
Sub Fertility**

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Discipline of Obstetrics and Gynaecology

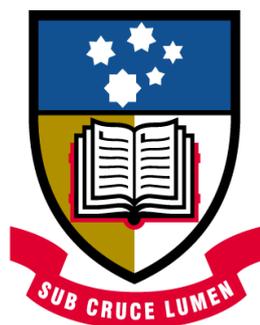
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Table of Contents

Table of Contents	3
Declaration.....	13
Abstract	14
Acknowledgements.....	17
Publications arising from this Thesis.....	19
Abstracts arising from this Thesis	20
List of Tables	22
List of Figures	25
1 Literature Review.....	28
1.1 INTRODUCTION	29
1.2 CLASSIFICATION OF OVERWEIGHT AND OBESITY	30
1.3 MALE REPRODUCTIVE SYSTEMS.....	30
1.3.1 Testicular function and spermatogenesis.....	30
1.3.2 Hormonal regulation of spermatogenesis	36
1.4 SPERM CONTRIBUTION TO EARLY EMBRYO DEVELOPMENT.....	38
1.4.1 Post ejaculation sperm activation.....	38
1.4.2 Fertilisation	38
1.4.3 Early embryo development	39
1.5 DIAGNOSIS OF MALE SUB FERTILITY	41

1.6	IMPACT OF MALE OBESITY ON SPERM FUNCTION AND HEALTH	42
1.6.1	WHO sperm parameters	42
1.6.2	Male obesity on sperm DNA integrity and oxidative stress	45
1.6.3	Male obesity on additional markers of sperm function	46
1.6.4	Proposed mechanisms by which obesity alters sperm function	47
1.7	PATERNAL PROGRAMMING	53
1.7.1	Paternal obesity programs embryos, pregnancy and offspring health	54
1.7.2	Proposed transmission of altered offspring health	58
1.8	REVERSIBILITY	62
	64
1.8.1	Diet and exercise	65
1.9	CONCLUSION.....	68
1.10	RESEARCH HYPOTHESIS AND AIMS.....	68
1.11	REFERENCES	71
1.12	STATEMENT OF AUTHORSHIP	102
1.13	PUBLISHED VERSION OF LITERATURE REVIEW	103
2	Diet and exercise in an obese mouse fed a high fat diet improves metabolic health and reverses perturbed sperm function.....	113
2.1	STATEMENT OF AUTHORSHIP	114
2.2	ABSTRACT.....	115
2.3	INTRODUCTION	116
2.4	METHODS.....	118

2.4.1	Animals and Diet.....	118
2.4.2	Exercise Intervention (Swimming).....	118
2.4.3	Body Composition.....	119
2.4.4	Metabolites, Corticosterone and Testosterone analysis	119
2.4.5	Glucose Tolerance Test (GTT) and Insulin Tolerance Test (ITT).....	120
2.4.6	Collection of Mouse Sperm.....	120
2.4.7	Sperm Count, Motility and Morphology	120
2.4.8	Sperm Binding	121
2.4.9	Capacitation and Acrosome Reaction.....	121
2.4.10	TUNEL.....	122
2.4.11	MitoSOX Red.....	122
2.4.12	RedoxSensor Red CC-1	122
2.4.13	Mitochondrial Membrane Potential (MMP) (JC-1).....	123
2.4.14	Glucose and Fructose Uptake	123
2.4.15	Statistical Analysis	124
2.5	RESULTS	125
2.5.1	Effect of diet and exercise on whole body physiology.....	125
2.5.2	Effect of diet and exercise on fasting blood glucose, glucose tolerance and insulin tolerance.....	126
2.5.3	Effect of diet and exercise on blood lipids	127
2.5.4	Effect of diet and exercise on serum corticosterone	127
2.5.5	Effect of diet and exercise on serum testosterone	128

2.5.6	Effect of diet and exercise on basic sperm parameters	128
2.5.7	Effect of diet and exercise on sperm capacitation and oocyte binding.....	128
2.5.8	The effect of diet and exercise on sperm oxidative stress	129
2.5.9	The effect of diet and exercise on sperm DNA integrity	129
2.5.10	The effect of diet and exercise on sperm metabolism.....	130
2.5.11	Physiology and sperm function	130
2.6	DISCUSSION	132
2.7	ACKNOWLEDGEMENTS	138
2.8	TABLES.....	140
2.9	FIGURES.....	144
2.10	REFERENCES	155
2.11	CHAPTER 2 PUBLISHED PAPER	166
3	Improving metabolic health in obese male mice via diet and exercise restores embryo development and fetal growth	180
3.1	STATEMENT OF AUTHORSHIP.....	181
	181
3.2	LINKING TO CHAPTER 3	182
3.3	ABSTRACT.....	183
3.4	INTRODUCTION	184
3.5	METHODS.....	186
3.5.1	Ethics Statement.....	186
3.5.2	Animals and Diet.....	186

3.5.3	Exercise Intervention (Swimming).....	187
3.5.4	Body Composition.....	187
3.5.5	Serum Metabolite Analysis	188
3.5.6	Intraperitoneal Glucose Tolerance Test (GTT) and Insulin Tolerance Test (ITT).	188
3.5.7	Embryo Collection.....	189
3.5.8	Embryo Culture	189
3.5.9	E-cadherin in Embryos.....	190
3.5.10	Blastocyst DNA Damage	190
3.5.11	Assessment of ICM, Trophectoderm and Epiblast Cell Number (Nanog and Oct4 Staining).....	191
3.5.12	Embryo Transfer	192
3.5.13	Statistical Analysis	192
3.6	RESULTS	194
3.6.1	Effect of Diet and Exercise on Embryo Development	194
3.6.2	Effect of Diet and Exercise on Blastocyst Cell Numbers and DNA Damage ..	194
3.6.3	Effect of Diet and Exercise on Epiblast, ICM and Trophectoderm Cell Number...	195
3.6.4	Effect of Diet and Exercise on Embryo Cell to Cell Contact.....	195
3.6.5	Effect of Diet and Exercise on Implantation and Fetal Viability	196
3.6.6	Associations between Paternal Metabolic and Hormonal state and Embryo and Fetal Growth and Development.....	197

3.7	DISCUSSION	199
3.8	TABLES	207
3.9	FIGURES.....	210
3.10	SUPPLEMENTARY TABLES	212
3.11	REFERENCES	218
3.12	CHAPTER 3 PUBLISHED PAPER	228
4	An obese father's metabolic state, adiposity and reproductive capacity indicate a son's reproductive health.....	238
4.1	STATEMENT OF AUTHORSHIP	239
4.2	LINKING TO CHAPTER 4	240
4.3	CAPSULE.....	241
4.4	ABSTRACT.....	241
4.5	INTRODUCTION	242
4.6	MATERIALS AND METHODS	244
4.6.1	Founder Animals and Diet	244
4.6.2	Generation/Sampling of F1 Males	245
4.6.3	Sperm Collection, Count, Motility and Morphology Analysis	245
4.6.4	F1 Male Sperm Binding	246
4.6.5	F1 Male Sperm Capacitation and Acrosome Reaction	246
4.6.6	F1 Male Sperm Mitochondrial Membrane Potential (MMP) (JC-1).....	246
4.6.7	Adiposity and Reproductive Organ Measurement	247
4.6.8	Testosterone Analysis	247

4.6.9	Statistical Analysis	247
4.7	RESULTS	249
4.7.1	Effect of Diet and Exercise on Founder Metabolism and Sperm Parameters	249
4.7.2	Effect of Founder Diet and Exercise on F1 Conventional Sperm Parameters	249
4.7.3	Effect of Founder Diet and Exercise on F1 Sperm Capacitation and Oocyte Binding	250
4.7.4	Effect of Founder Diet and Exercise on F1 Sperm Mitochondrial Parameters	251
4.7.5	Effect of Founder Diet and Exercise on F1 Male Reproductive Body Composition and Serum Testosterone	251
4.7.6	Correlations of Founder Adiposity and Metabolic status with F1 Reproductive Function	251
4.7.7	Correlations of Founder Reproductive Function with F1 Reproductive Function	252
4.8	DISCUSSION	253
4.9	ACKNOWLEDGEMENTS	258
4.10	FUNDING	259
4.11	TABLES	260
4.12	SUPPLEMENTARY TABLE	264
4.13	REFERENCES	265
4.14	CHAPTER 4 PUBLISHED PAPER	271
5	Preconception diet and exercise interventions in obese fathers rescues sperm microRNA profile, insulin resistance and obesity in female offspring	281

5.2	STATEMENT OF AUTHORSHIP	282
5.3	LINKING TO CHAPTER 5	283
5.4	ABSTRACT.....	284
5.5	ONE SENTENCE SUMMARY	284
5.6	INTRODUCTION	285
5.7	ADIPOSITY AND METABOLIC HEALTH OF OFFSPRING IN RESPONSE TO FOUNDER DIET AND/OR EXERCISE INTERVENTIONS	286
5.7.1	High Fat Diet (HH):	286
5.7.2	Diet alone (HC):.....	287
5.7.3	Exercise alone (HE):.....	289
5.7.4	Combined diet/exercise (HCE):	290
5.8	PATERNAL EPIGENETIC SIGNALS: SPERM MICRORNA PROFILES	291
5.9	PATERNAL GLYCAEMIA AND CORTICOSTERONE IS ASSOCIATED WITH SPERM MICRORNA LEVELS AND FEMALE OFFSPRING PHENOTYPES	293
5.10	CONCLUDING REMARKS	294
5.11	ACKNOWLEDGMENTS:	295
5.12	MATERIALS AND METHODS	296
5.12.1	Founder Animals and Diet	296
5.12.2	Exercise Intervention (Swimming)	296
5.12.3	Founder Body Composition	297
5.12.4	Founder Glucose Tolerance Test (GTT) and Insulin Tolerance Test (ITT)	297
5.12.5	Natural Mating to produce F1 females	298

5.12.6	F1 Female Body Composition.....	298
5.12.7	F1 Female GTT and ITT	299
5.12.8	F1 Female Insulin Response during a GTT	299
5.12.9	Metabolites and Hormone Analysis.....	300
5.12.10	Histology of F1 Female Gonadal Adiposity	300
5.12.11	MicroRNA analysis of Founder Sperm.....	301
5.12.12	Statistical Analysis	302
5.13	TABLES.....	304
5.14	FIGURES.....	305
5.15	SUPPLEMENTARY TABLES	310
5.16	SUPPLEMENTARY FIGURES	324
5.17	REFERENCES	328
6	Final Discussion.....	333
6.1	INTRODUCTION	334
6.2	DIET AND EXERCISE INTERVENTIONS IN OBESE FOUNDERS	335
6.2.1	Improvements to founder metabolic status	335
6.2.2	Restoration of sperm function and early embryo/fetal development	336
6.2.3	Partial rescue of offspring programming phenotype.....	339
6.2.4	Partial normalisation of microRNA abundance in sperm – a potential mechanism	342
6.3	DOES FOUNDER ADIPOSITY ALONE EXPLAIN THE OBSERVED EFFECTS?.	346

6.3.1	Are circulating lipids and metabolites a better biomarker for predicting altered sperm function and subsequent embryo and offspring health?	348
6.3.2	How blood metabolites and lipid profiles associated with obesity might alter the epigenetic status of sperm.....	350
6.4	LIMITING FACTORS OF RODENT MODELS AND ALTERNATIVE PARADIGMS OF DIET AND EXERCISE INTERVENTIONS	355
6.4.1	Limitations	355
6.4.2	Alternative paradigms	356
6.5	CONCLUDING REMARKS AND FUTURE DIRECTIONS	357
6.6	REFERENCES	359
7	Appendix.....	370
7.1	MODIFIED G-IVF COMPOSITION	371
7.2	GLUCOSE AND FRUCTOSE UPTAKE EQUATIONS.....	372
7.3	PHOSPHATE BUFFERED SALINE.....	373
7.4	SALINE FOR INJECTION.....	373
7.5	AVERTIN ANAESTHETIC	373
7.6	TAQMAN PROBES	374

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Nicole McPherson

Wednesday, 10th September 2014

Abstract

Male overweight/obesity affects 70% of the adult Australian population with this rate 10% higher (80%) in men attending a South Australian fertility clinic, suggesting a link between male overweight/obesity and sub fertility. Male obesity alters the molecular structure of sperm, increasing sperm DNA damage and reactive oxygen species (ROS) and altering mitochondrial function. This perturbed sperm function leads to altered embryo quality (reduced blastocyst development, blastocyst cell numbers and blastocyst mitochondrial function) which subsequently reduces implantation and live birth rates. Rodent models of male obesity have further implicated male obesity in the development of adult chronic diseases, increasing the susceptibility of obesity, diabetes and sub fertility in offspring across two generations.

Limited published research has assessed the reversibility of male obesity induced sub fertility. Due to limitations inherited in human studies, the aim of this thesis was to establish if obesity induced sub fertility could be reversed utilising a rodent model of male obesity with short term diet and/or exercise interventions for proof of concept. Male mice were fed a high fat diet (HFD) containing 21% fat or a control diet (CD) containing 6% fat for a period of 8-10 weeks to increase adiposity, following HFD exposure mice were allocated to one of four treatment groups 1) diet intervention (HC, change to CD), 2) exercise intervention (HE, continuation of a HFD with 3 x 30 min swimming sessions a week), 3) combined diet/exercise intervention (HCE, change to a CD with swimming exercise) or 4) continuation of a HFD (HH) for a further 8-10 weeks. Mice allocated to the CD continued on the CD (CC) for intervention period.

Diet intervention with (HCE) or without (HC) exercise reduced bodyweight, adiposity, and serum cholesterol while exercise intervention alone (HE) maintained their original level of adiposity. All interventions had improvements to serum glucose and leptin regulation while exercise subsequently improved serum free fatty acids and C - reactive protein. All interventions restored sperm function (motility, morphology, mitochondrial function, ROS and DNA damage levels). Males were subsequently mated with super ovulated normal weight females for assessment of embryo quality. All interventions restored blastocyst cell numbers and day 18 fetal weights while, exercise with (HCE) or without (HE) as CD further restored embryo development. As early embryo and fetal health are predictors of subsequent offspring health, males were also mated with naturally cycling normal weight females to produce offspring. Diet intervention alone (HC) showed the biggest restorations to male offspring sperm function (motility, sperm binding, capacitation and mitochondrial function). In contrast, exercise intervention alone (HE) showed the biggest restoration to female offspring metabolic health (glucose and insulin sensitivity and adipose accumulation) while the remaining interventions (HC and HCE) had minimal impact. The improvements to female offspring metabolic health from exercise interventions in their fathers may be related to their partial restoration of sperm X-linked microRNA abundance (i.e. mir-503 and mir-465b-5p), with these microRNAs specifically targeting pathways important for early embryo development including cell cycle control and apoptosis.

Together these studies provided some of the first evidence for the reversibility of obesity related fertility issues in males, highlighting that it may be more about restoring systematic metabolic health rather than a reduction in adiposity, with the deciphering an epigenetic mechanism in sperm for transmission of effects to the embryo and offspring phenotypes. These studies will undoubtedly stimulate further research into other related molecular mechanisms and the

independent associations between obesity related metabolic changes and their relationships with male fertility.

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Publications arising from this Thesis

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'**N. O. Palmer**, H.W. Bakos, J.A. Owens, B.P. Setchell and M.Lane (2012) 'Diet and exercise in an obese mouse fed a high fat diet improves metabolic health and reverses perturbed sperm function', **American Journal of Physiology Endocrinology and Metabolism**, Apr 1; 302 (7): E768-80

N. O. McPherson, H. W. Bakos, J .A. Owens, B. P. Setchell and M. Lane (2013) 'Improving metabolic health in obese male mice via diet and exercise restores embryo development and fetal growth', **PLOS One**; Aug 19;8(8):e71459

N. O. McPherson, T. Fullston, H. W. Bakos, B. P. Setchell and M. Lane (2014) 'An obese father's metabolic state, adiposity and reproductive capacity which are improved by diet and/or exercise indicates a son's reproductive health', **Fertility and Sterility**; Mar; 101 (3): 865-73

Abstracts arising from this Thesis

N. O. Palmer, H. W. Bakos, B. P. Setchell and M. Lane (2011) 'Diet and exercise improves sperm function in obese mice', SRB, Cairns

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N. O. Palmer, Hassan W Bakos, Julie A Owens, Brian P Setchell and Michelle Lane (2012) 'Exercise and to a lesser extent a low fat diet in obese fathers restores metabolic health of subsequent offspring', Biology of Reproduction, SSR 2012, Penn State University

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List of Tables

Table 1.1 Lower reference limits (5 th centiles and their 95% confidence intervals) for semen characteristics and diagnosis of male sub fertility.....	41
Table 1.2 Summary of studies investigating male obesity and its effect on WHO sperm parameters.....	44
Table 2.1: Composition of animal diets.....	140
Table 2.2: The effect of diet and exercise on body composition.....	141
Table 2.3: The effect of diet and exercise on blood metabolites, corticosterone and testosterone levels post intervention.....	142
Table 2.4: The effect of diet and exercise on simple sperm parameters.....	143
Table 3.1: The effect of diet and exercise of obese males on embryo development.....	207
Table 3.2: The effect of diet and exercise of obese males on blastocyst development.....	208
Table 3.3: The effect of diet and exercise of obese males on subsequent implantation and fetal development.....	209
Table S3.1: Composition of animal diets.....	212
Table S3.2: Numbers of embryos and pups derived from each father.....	213
Table S3.3: The effect of diet and exercise on founder male body composition after intervention.....	215
Table S3.4: The effect of diet and exercise on founder male serum metabolites after intervention.....	216
Table S3.5 Correlations between founder metabolite concentrations and blastocyst and fetal health independent of founder adiposity.....	217
Table 4.1: Effect of diet and exercise on founder adiposity, serum metabolites and reproductive measures.....	260

Table 4.2: Effect of founder diet and exercise on F1 sperm function.....	261
Table 4.3: Effect of founder diet and exercise on F1 male reproductive organs and testosterone.....	262
Table 4.4: Founder metabolic and reproductive health correlate with F1 reproductive measures.....	263
Table S4.1: Composition of animal diets.....	264
Table 5.1: Paternal glycaemia, plasma corticosterone and C - reactive protein correlate with founder sperm microRNAs and female offspring phenotypes independent of treatment.....	304
Table S5.1: Composition of animal diets	310
Table S5.2: Effect of diet and exercise on founder body composition, metabolism and hormones.....	311
Table S5.3: Effect of founder diet and exercise interventions on F1 female body composition, metabolites and hormones at 10 weeks of age.....	313
Table S5.4: Effect of founder diet and exercise interventions on F1 female body composition, metabolites and hormones at 18 weeks of age	314
Table S5.5: Effect of founder diet and exercise interventions on F1 female body composition, metabolites and hormones at 28 weeks of age	315
Table S5.6: X-linked microRNAs in sperm from control and high fat diet founders 10 weeks pre-intervention.....	316
Table S5.7: Confirmed gene targets of X-linked microRNAs change in sperm of HH founders	318
Table S5.8: Number of successful matting's per founder male.....	322
Table S5.9: Effect of diet and exercise on founder time to mate, mating rates, litter size and sex ratio.....	323

Table 7.1: Media composition of modified G-IVF medium371

Table 7.2: TaqMan PCR probes used for confirmation of microRNA PCRs in
sperm.....374

List of Figures

Figure 1.1: Cells of the testes.....	31
Figure 1.2: Stages of spermatogenesis.....	35
Figure 1.3: Hormonal regulation of spermatogenesis.....	37
Figure 1.4: Changes to hormonal regulation resultant from male obesity.....	50
Figure 1.5: Hypothesis for the improvement to fertility in obese male's via weight loss through diet and exercise interventions.....	64
Figure 2.1: Abnormal mouse sperm morphology classifications.....	144
Figure 2.2: Weight gained/lost post and pre intervention periods.....	145
Figure 2.3: The effect of diet and exercise on glucose and insulin tolerance.....	146
Figure 2.4: The effect of diet and exercise on sperm capacitation and binding.....	148
Figure 2.5: The effect of diet and exercise on sperm DNA damage and oxidative stress.....	149
Figure 2.6: The effect of diet and exercise on sperm metabolism.....	151
Figure 2.7: Metabolic and lipid status and sperm function.....	153
Figure 3.1: E-cadherin staining patterns.....	210
Figure 3.2: The effect of diet and exercise of obese males on e-cadherin staining patterns in compacting embryos.....	211
Figure 5.1: The effect of diet and exercise in diet induced paternal obesity on adiposity and plasma triglyceride in female offspring.....	305
Figure 5.2: The effects of diet and exercise in diet induced paternal obesity on insulin sensitivity, glucose tolerance and insulin secretion in female offspring.....	307
Figure 5.3: The effect of diet and exercise interventions in diet induced paternal obesity on X-linked sperm microRNAs.....	309

Figure S5.1: Paternal diet and exercise as obesity interventions on growth rate pre and post intervention.....324

Figure S5.2: The effect of paternal diet and exercise as obesity interventions on female offspring pre-weaning growth.....325

Figure S5.3: The effect of paternal diet and exercise interventions as obesity interventions on female offspring post weaning growth.....326

Figure S5.4: The effect of paternal diet and exercise as obesity interventions on X-linked sperm microRNAs.....327

Figure 6.1 Summary of outcomes from diet and exercise interventions in obese males on their metabolic health, sperm function, subsequent early embryo development and offspring health345

Figure 6.2 Hypothesis of how changes to circulating lipids and metabolites may change the epigenetic status of sperm that might ultimately form the basis for offspring programming.....354

Figure 7.1 The two step equation illustrating the conversion of the non-fluorescent NADP⁺ to the fluorescent NADPH.....372

Figure 7.2 The three step equation illustrating the conversion of fructose-6-P to glucose-6-P, and then non-fluorescent NADP⁺ to the fluorescent NADPH.....372