Association of Dietary Patterns and Macronutrient Intake with Type 2 Diabetes Risk

Amani Alhazmi (MFoodSc)

A thesis submitted in fulfilment of the requirement to obtain the degree of Doctor of Philosophy in Nutrition and Dietetics

School of Health Sciences, Faculty of Health and Medicine, University of Newcastle, Australia

May 2014
Statements

Statement of Originality

This thesis contains no material which has been accepted for the award of any other degree or diploma 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. I give consent to this copy of my thesis, when deposited in the University Library**, being made available for loan and photocopying subject to the provisions of the Copyright Act 1968.

**Unless an Embargo has been approved for a determined period.

Statement of Collaboration

I hereby certify that the work embodied in this thesis has been done in collaboration with other researchers. I have included as part of my thesis a statement clearly outlining the extent of the collaboration, with whom and under what auspices.

Statement of Authorship

I hereby certify that this thesis is in the form of a series of published papers of which I am a joint author. I have included as part of my thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

Signed:

Amani Alhazmi
Acknowledgements

First and foremost all praise is due to Allah who blessed me with the opportunity to undertake this research. Without whose grace this work would have not been accomplished.

I wish to express sincere gratitude to my PhD supervisors: Prof. Manohar Garg for his invaluable guidance, expertise, and accessibility which have helped me to grow independently as a researcher; Dr. Elizabeth Stojanovski for her statistical expertise, her thorough reviewing of all my papers, and for being so patient with my unending statistical queries; Mr. Mark McEvoy for his supervisory input early in the PhD candidature, critical thinking skills, and ongoing support throughout the duration of this project. I was very fortunate to be working under their supervision.

I wholeheartedly appreciate the participants of the Australian Longitudinal Study on Women’s Health (ALSWH) and Hunter Community Study (HCS), who have generously provided their time, personal information and support for the research. I would like also to thank the ALSWH and HCS research teams for providing the data for this thesis. Thank you especially, to Prof. Wendy Brown for her kindly advice in ALSWH data and valuable feedback, and Professor Graham Giles of the Cancer Epidemiology Centre of Cancer Council Victoria, for permission to use the Dietary Questionnaire for Epidemiological Studies (Version 2), Melbourne: Cancer Council Victoria, 1996. I would like to acknowledge the financial support from the ministry of Higher education in Saudi Arabia for providing me a scholarship to undertake this PhD.

Thank you to Nutraceuticals Research Group members, both past and present, for sharing this journey with me, particularly Dr. Irene Munro and Cintia Dias for offering help whenever I needed it. I would also like to express my appreciation to my friends Dr. Jency Thomas and Nouf Albadi for their constant encouragement, unyielding support and friendship.
I also wish to extend thanks to my family in Saudi Arabia, including my parents Hamad and Samira Alhazmi and my siblings for their emotional support, ongoing encouragement and belief in me.

Lastly and most importantly, I owe my greatest debts and thanks to my dearest husband Abdullah Alharbi for his enduring love, support and care, I would not have made it here without him. I would like to express my gratitude and guilt to my daughters Ghala, Juri and Tahlia. I am grateful to them for their patience while I was absent from their lives due to my busy and stressful PhD journey.
Relevant Publications

Research Publications Central to this Thesis


Additional Publications Associated with Thesis (Appendixes 6 and 7)


**Conference Presentation with Published Abstracts**


4. **Alhazmi A**, Stojanovski E, McEvoy M, Garg ML, Overall Diet Quality Score and Type 2 Diabetes, The Australian Diabetes Society (ADS) and Australian Diabetes Educators Association (ADEA) annual scientific meeting, Gold Coast, Queensland, Australia, August 2012, Conference Proceedings.

5. **Alhazmi A**, Stojanovski E, McEvoy M, Garg ML, ARFS Items and Type 2 Diabetes in Australian Women, The Australian Diabetes Society (ADS) and Australian Diabetes Educators Association (ADEA) annual scientific meeting, Gold Coast, Queensland, Australia, August 2012, Conference Proceedings.


10. **Alhazmi A**, Stojanovski E, McEvoy M, Garg ML, Total carbohydrate intake does not predict type 2 diabetes risk in mid-age women from the Australian longitudinal study on women’s Health, The Australian Diabetes Society (ADS) and Australian Diabetes Educators Association (ADEA) annual scientific meeting, Sydney, NSW, Australia, August 2013, Conference Proceedings.


# Contents

Statements ....................................................................................................................................... ii  
Statement of Originality .................................................................................................................... ii  
Statement of Collaboration ................................................................................................................. ii  
Statement of Authorship .................................................................................................................... ii  

Acknowledgements ......................................................................................................................... iii  

Relevant Publications ....................................................................................................................... v  
Research Publications Central to this Thesis ...................................................................................... v  
Conference Presentation with Published Abstracts ............................................................................. vi  

Contents .......................................................................................................................................... ix  

List of Tables .................................................................................................................................... xiv  

List of Figures .................................................................................................................................. xv  

List of Abbreviations ....................................................................................................................... xvi  

Synopsis .......................................................................................................................................... xviii  

Chapter 1: General Introduction ..................................................................................................... 1  
1.1 Thesis Outline ............................................................................................................................ 1  
1.2 Background .................................................................................................................................. 2  
  1.2.1 Definition of Type 2 Diabetes ............................................................................................... 2  
  1.2.2 Epidemiology and Health Problems .................................................................................... 3  
  1.2.3 Aetiology of Type 2 Diabetes ............................................................................................... 3  
  1.2.4 Diet and Development of Type 2 Diabetes ........................................................................ 5  
1.3 Research Aims ............................................................................................................................. 6  
1.4 Research Questions ...................................................................................................................... 7  

Chapter 2: General Methods ........................................................................................................... 9  
2.1 Systematic Literature Reviews and Meta-Analysis ................................................................... 9  
2.2 Prospective Cohort Studies ......................................................................................................... 9
2.2.1 Ethics Approval .................................................................11
2.2.2 Data Acquisition .............................................................11
2.2.3 Dietary Assessment .........................................................12
2.2.4 Statistical Methods .........................................................13

2.3 Nested Case-control Study ......................................................13
2.3.1 Ethics Approval .............................................................14
2.3.2 Data Acquisition .............................................................15
2.3.3 Blood Collection and Whole Blood Fatty Acid Measurement ....15
2.3.4 Statistical Methods .........................................................15

Chapter 3: Literature Review ..........................................................16

3.1 Macronutrient Intakes and Development of Type 2 Diabetes: A Systematic Review and Meta-Analysis of Cohort Studies .........................................................16
3.1.1 Abstract ................................................................................16
3.1.2 Introduction ...........................................................................17
3.1.3 Methods ...............................................................................18
3.1.4 Results ..................................................................................20
3.1.5 Discussion ............................................................................40
3.1.6 Conclusion ............................................................................45

3.2 The Association between Dietary Patterns and Type 2 Diabetes: A Systematic Review and Meta-Analysis of Cohort Studies .........................................................46
3.2.1 Abstract ..............................................................................46
3.2.2 Introduction ...........................................................................47
3.2.3 Material and Methods ..........................................................47
3.2.4 Results ..................................................................................50
3.2.5 Discussion ............................................................................58
3.2.6 Conclusions .........................................................................60

Chapter 4: Macronutrient Intake and Type 2 Diabetes Risk in Middle-Aged Australian Women. Results from the Australian Longitudinal Study on Women’s Health ............61
Chapter 6: Methods

6.3.2 Dietary Intake ..................................................................................................94
6.3.3 Diet-quality Scores ..........................................................................................94
6.3.4 Ascertainment of Type 2 Diabetes .................................................................96
6.3.5 Assessment of Covariates .............................................................................96
6.3.6 Statistical Analysis .........................................................................................97

6.4 Results ..................................................................................................................97
6.5 Discussion .............................................................................................................102

Chapter 7: General Discussion .................................................................................106

7.1 Chapter Summary ...............................................................................................106
7.2 Key Findings .......................................................................................................106
    7.2.1 Chapter 3 Findings .....................................................................................106
    7.2.2 Chapter 4 Findings .....................................................................................107
    7.2.3 Chapter 5 Findings .....................................................................................109
    7.2.4 Chapter 6 Findings .....................................................................................109

7.3 Research Strengths and Limitations ....................................................................110
    7.3.1 Strengths .....................................................................................................110
    7.3.2 Limitations ..................................................................................................112

7.4 Implications for Nutrition Research ....................................................................112
7.5 Conclusion ...........................................................................................................114

References ...............................................................................................................115

Appendices ..............................................................................................................135

Appendix 1: Co-author Statement for Chapter 3 (Section 3.1) ................................135
Appendix 2: Co-author Statement for Chapter 3 (Section 3.2) ..............................137
Appendix 3: Co-author Statement for Chapter 4 ....................................................138
Appendix 4: Co-author Statement for Chapter 5 ....................................................139
Appendix 5: Co-author Statement for Chapter 6 ....................................................140
Appendix 6: Additional Publications Associated with Thesis ...............................141
Appendix 7: Additional Publications Associated with Thesis ...............................150
List of Tables

Table 1: Classification Values for the Oral Glucose Tolerance Test.............................................2
Table 2: Research Aims and Research Questions by Chapter .......................................................8
Table 3: Prospective Cohort Studies of Macronutrients ..............................................................26
Table 4: Stratified Pooled Risk Estimates and 95% Confidence Intervals for Macronutrient and Type 2 Diabetes.....................................................................................................................36
Table 5: Description of Prospective Cohort Studies of Dietary Patterns Identified via the Systematic Review..................................................................................................................52
Table 6: Baseline Characteristics of 8370 Middle-Age Australian Women who Completed the Third Survey of ALSWH in 2001 According to Quintiles of Dietary macronutrient Intakes ...........................................................................................................................................68
Table 7: Relative Risk of Type 2 Diabetes by Quintiles of Macronutrient Intake among Middle-Aged Australian Women from ALSWH, 2001-2007 .......................................................71
Table 8: Relative Risk of Type 2 Diabetes by quintiles of fatty acid intakes among Middle-Aged Australian Women from ALSWH .................................................................................................72
Table 9: Baseline Characteristics of the Study Population (N= 187) from the Hunter Community Study ..................................................................................................................................................84
Table 10: Odds Ratios (and 95% CIs) for Incident Diabetes by Whole Blood Fatty Acids, Hunter Community Study .........................................................................................................................85
Table 11: Fatty Acid Desaturase Products in Fasting Whole Blood of Type 2 Diabetes Cases Compared with Control, Hunter Community Study 1 ..................................................................................86
Table 12: Baseline Characteristics of the 8370 Middle-Aged Women who completed the Third Survey of the ALSWH (Australian Longitudinal Study on Women’s Health) According to First (Q1) and Fifth (Q5) Quintiles of Australian Recommended Food Score (ARFS) and Dietary Guideline Index (DGI) ........................................................................................................99
Table 13: OR of Type 2 Diabetes risk by quintiles of the Australian Recommended Food Score (ARFS) and Dietary Guideline Index (DGI) among middle-aged Australian women participating in the ALSWH (Australian Longitudinal Study on Women’s Health) ..........101

List of Figures

Figure 1: Flow chart of participant’s selection from ALSWH for the analysis .........................11
Figure 2: Flow chart of participant’s selection from HCS for the analysis .................................14
Figure 3: Forest plot displaying relative risk (RR) and 95% CI for type 2 diabetes incidence for high carbohydrates intake diets compared with diabetes incidence for low carbohydrate intake diets ............................................................................................................................38
Figure 4: Forest plot displaying RR and 95% CI for type 2 diabetes incidence for high total and/or subtype dietary fat intake compared with type 2 diabetes incidence for low total and/or subtype dietary fat intake. .................................................................................................................................39
Figure 5: Forest plot displaying RR and 95% CI for diabetes incidence for high total and/or subtype dietary protein intake compared with diabetes incidence for low total and/or subtype dietary protein intake. ..........................................................................................................................40
Figure 6: Flow diagram of the systematic review of the association between dietary patterns and type 2 diabetes. NHS, Nurses’ Health Study .................................................................................................................................51
Figure 7: Forest plot displaying RR and 95% CI for type 2 diabetes incidence for the highest vs the lowest intake of healthy dietary patterns. .................................................................................................57
Figure 8: Forest plot displaying RR and 95% CI for type 2 diabetes incidence for the highest vs the lowest intake of unhealthy dietary patterns. ...............................................................................................58
**List of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHEI</td>
<td>Alternate healthy eating index</td>
</tr>
<tr>
<td>ALA</td>
<td>Alpha-linolenic acid (18:3 n-3)</td>
</tr>
<tr>
<td>ALSWH</td>
<td>Australian Longitudinal Study on Women’s Health</td>
</tr>
<tr>
<td>ARA</td>
<td>Arachidonic acid (20:4n-6)</td>
</tr>
<tr>
<td>ARFS</td>
<td>Australian Recommended Food Score</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COX</td>
<td>Cyclooxygenase</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DASH</td>
<td>dietary approach to stop hypertension</td>
</tr>
<tr>
<td>DGI</td>
<td>Dietary Guideline Index</td>
</tr>
<tr>
<td>DGLA</td>
<td>Dihomo-gamma-linolenic acid (20:3n-6)</td>
</tr>
<tr>
<td>DHA</td>
<td>Docosahexaenoic acid (22:6n-3)</td>
</tr>
<tr>
<td>DPA</td>
<td>Docosapentaenoic acid (22:5n-3)</td>
</tr>
<tr>
<td>EPA</td>
<td>Eicosapentaenoic acid (20:5n-3)</td>
</tr>
<tr>
<td>FFA</td>
<td>Free fatty acid</td>
</tr>
<tr>
<td>FFQ</td>
<td>Food frequency questionnaire</td>
</tr>
<tr>
<td>GFPI</td>
<td>German food pyramid index</td>
</tr>
<tr>
<td>H&amp;L</td>
<td>Hosmer and Lemeshow's goodness-of-fit test</td>
</tr>
<tr>
<td>HCS</td>
<td>Hunter Community Study</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>IC</td>
<td>Akaike’s information criterion test</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>IR</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>LNA</td>
<td>Linoleic acid (18:2n-6)</td>
</tr>
<tr>
<td>MDS-2</td>
<td>Mediterranean diet score</td>
</tr>
<tr>
<td>MUFA</td>
<td>Monounsaturated fatty acid</td>
</tr>
<tr>
<td>n-3 PUFA</td>
<td>Total omega-3 polyunsaturated fatty acid</td>
</tr>
<tr>
<td>n-6 PUFA</td>
<td>Total omega-6 polyunsaturated fatty acid</td>
</tr>
<tr>
<td>OCP</td>
<td>Oral contraceptive pill</td>
</tr>
<tr>
<td>OLA</td>
<td>Oleic acid (C18:1n-9)</td>
</tr>
<tr>
<td>OR</td>
<td>Odd ratio</td>
</tr>
<tr>
<td>PAM</td>
<td>Palmitic acid (16:0)</td>
</tr>
<tr>
<td>PUFA</td>
<td>Polyunsaturated fatty acids</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical Analysis Systems</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SFA</td>
<td>Saturated fatty acid</td>
</tr>
<tr>
<td>STA</td>
<td>Stearic acid (18:0)</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Synopsis

Type 2 diabetes is a pervasive health crisis that threatens all nations. The epidemic has grown in parallel with the increase in obesity due to different factors, including nutrition transition. This thesis comprises four interconnected research stages that aim to contribute to the evidence base informing associations of dietary patterns and macronutrient intake in relation to type 2 diabetes risk.

The first aim of this thesis was to review the existing evidence for the association of macronutrients and dietary patterns with type 2 diabetes risk by conducting two systematic literature reviews and meta-analyses. The existing evidence on the association of macronutrient intake and dietary patterns with type 2 diabetes risk was synthesised (Chapter 3). The first review found that while total carbohydrate is associated with an increased risk of type 2 diabetes, high vegetable fat intake may decrease the risk. The evidence from the second review showed that adherence to a healthy dietary pattern was inversely associated with type 2 diabetes risk, whereas an unhealthy dietary pattern was positively associated with the disease. These reviews highlighted the need for well-designed prospective cohort studies to further examine these associations.

The second aim was to investigate the association between macronutrient intake and type 2 diabetes in middle-aged Australian women. A prospective cohort study of 8370 Australian women from the Australian Longitudinal Study on Women’s Health (ALSWH) aged 45–50 years and free of type 2 diabetes at baseline with six years (2002–2007) of follow up was undertaken (Chapter 4). Dietary intake was assessed with a self-reported validated food frequency questioner (FFQ) and the association between macronutrients and type 2 diabetes was investigated using multiple logistic regressions adjusted for potential confounding variables. After the six-year follow-up, 311 women developed type 2 diabetes. The data indicate that consumption of monounsaturated fatty acid (MUFA), total omega-3 polyunsaturated fatty acid (n-3 PUFA), Alpha-linolenic acid (ALA), and omega-6 polyunsaturated fatty acid (n-6 PUFA) may increase the risk of developing type 2 diabetes in women.
The potential association between fatty acids and type 2 diabetes found in the above study was further investigated in a nested case-control study of 187 adults aged 55–85 years from the Hunter Community Study (HCS) (Chapter 5). The study aimed to examine the association of fasting whole blood fatty acid concentrations with incident type 2 diabetes. The results suggested that higher fasting whole blood concentrations of omega-6 polyunsaturated fatty acids (n-6PUFA) arachidonic acid (ARA) and dihomo-gamma-linolenic acid (DGLA) as well as ALA, Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) are associated with an increased risk of diabetes, whereas increased fasting whole blood concentrations of lignoceric acid is inversely associated with diabetes risk. These findings may negate previous evidence and emphasise the critical need for further investigations in this area.

Focus then shifted to investigate the association between diet and type 2 diabetes in a prospective cohort study using a complementary approach to determine the ability of two diet-quality scores to predict the incidence of type 2 diabetes (Chapter 6). The methods employed in this study were similar to those of the first prospective cohort study. The study suggested that the risk of type 2 diabetes in Australian women with the highest diet quality score as measured by the Dietary Guideline Index (DGI) was about 50% lower than those with the lowest diet quality score.

Taken together, the research outlined herein provides detailed data on the associations between macronutrient intake and dietary patterns in relation to type 2 diabetes risk. The thesis concludes with reflections on the implications of its findings for nutrition research and key recommendations for ongoing research in this area. It suggests that a well-designed, adequately powered intervention research investigating the effect of these dietary factors in relation to type 2 diabetes risk is necessary to form future recommendations on preventive dietary approaches.