Reproductive Factors and their Associations with

Osteoporosis and Osteoarthritis in Women

by

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Submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy

University of Tasmania

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Statement of Originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government’s Office of the Gene Technology Regulator and the Rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

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Statement of Co-Authorship

This thesis includes work which has been submitted for publication in peer-reviewed journals. Shuying Wei (SW) was not the sole author for the publication of the work and was assisted by the co-authors. The contributions of each author are detailed as follows.


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Details of the authors roles:

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GJ and RT participated in analysis and interpretation of data, and critically revised the manuscript.

TD contributed to study design and planning, interpretation of data and critically revised the manuscript.
AV contributed to study design and planning, participated in analysis and interpretation of data, assisted with the initial manuscript draft, and critically revised the manuscript.


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- CD participated in analysis of data, and critically revised the manuscript.
- SF and LL participated in data collection and critically revised the manuscript.
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Proportion of contribution:

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FC contributed to study design and planning, interpretation of data and critically revised the manuscript.

GJ contributed to study design and planning, participated in analysis and interpretation of data, assisted with the initial manuscript draft, and critically revised the manuscript.

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GJ participated in study design, analysis and interpretation of data, and critically revised the manuscript.

AV participated in study design, interpretation of data, and critically revised the manuscript.

FC and LM participated in study design and critically revised the manuscript.

PO participated in analysis and interpretation of the data, and critically revised the manuscript.

MC and MD participated in data collection and critically revised the manuscript.

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Alison Venn (Primary Supervisor)
Abstract

Women are at higher risk of both osteoporosis and osteoarthritis (OA) compared with age-matched males. Sex hormones and reproductive factors may partly explain these differences. This study therefore aimed to investigate reproductive factors including parity, menstrual regularity, use of oral contraceptives (OC) and hormone replacement therapy (HRT) and their associations with bone mass, cartilage and radiographic OA in population-based samples of both young and older women.

Young women aged 26 to 36 years were selected from the Childhood Determinants of Adult Health (CDAH) study, a 20-year follow-up of children who participated in 1985 Australian Schools Health and Fitness Survey (ASHFS). Older women aged 50 to 80 years were selected from the Tasmanian Older Adult Cohort (TASOAC) study, an ongoing prospective study in southern Tasmania. Parity, menstrual regularity and use of OC and HRT were assessed by self-administered questionnaire. Bone mass was measured by quantitative ultrasound (QU3) for young women and bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) for older women. Knee cartilage volume and cartilage defects were measured by magnetic resonance imaging (MRI) for both young and older women and radiographic OA was assessed by X-ray only for older women.

Key findings were:

- Young women:
  - Current use of OC was associated with higher bone mass.
  - Irregular menstrual cycles were associated with higher bone mass and the association was partially mediated by markers of androgen status especially free testosterone.
  - Parity was positively associated with cartilage defects primarily at the patella site. Women with three or more children had the highest prevalence of cartilage defects.
In older women:

- Ever use and duration of OC use were associated with higher BMD in the spine and total body measured at age 50-80 years.
- OC use for five to ten years was associated with a reduction of vertebral fracture.
- Parity was associated with lower cartilage volume primarily in the tibial compartment and the associations were dose-dependent.
- Parity was associated with higher cartilage defects only in the patella compartment.
- There were no associations between parity and osteophytes or joint space narrowing (JSN).
- Use of OC and HRT was not associated with knee cartilage volume, cartilage defects or radiographic OA including JSN and osteophytes.

In conclusion, these cross-sectional analyses of population-based samples of both young and older women showed use of OC was associated with higher bone mass suggesting a protective effect of OC use on bone health. In young women, menstrual irregularity was associated with alterations of sex hormones but may not be as harmful for bone mass as previously believed. Parity, particularly higher parity, was associated with higher cartilage defects in young women and low cartilage volume in older women indicating an effect of childbearing on the development of OA in women. A diagram below illustrated the main conclusions from this study.
Main conclusions of reproductive factors and their associations with bone mass and cartilage in both young and older women

Pink-face figures indicate factors selected from young women, yellow-face figures indicate factors selected from older women.
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First and foremost, I would like to express my greatest appreciation to my primary supervisor, Professor Alison Venn. This thesis would not have been accomplished without her guidance, encouragement, and even patient help with writing English. I have been working under her supervision since 2006 while I started doing my Honours. Her enthusiasm and passion for her work, extensive expertise in academic research and warm-hearted personality have deeply impressed me. She has helped not only in my academic development but also in getting the support of a scholarship, providing a work opportunity and financial support for attending a significant international conference. I feel extremely fortunate to have been a PhD student working under her supervision.

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I dedicate this thesis to my mother to commemorate such a kind woman. She 
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young girl but she was always very patient with her children, creating laughter in her 
family and providing help to the neighbours. Since I moved to Australia, she was always 
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communicating with English and even the western foods but she never complained that I 
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I would also like to sincerely express my great thanks to my father for his 
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Publications Arising from the Thesis


Chapter 8: Wei S, Jones G, Venn A, Cicuttini F, March L, Otahal P, Cross M, Dalton M, Dwyer T & Ding C. The association between parity and knee cartilage in young women. Manuscript has been accepted by the *Rheumatology* (ID: KES201).
Scientific Presentations Arising from the Thesis

2009
The 2nd Joint Meeting of the International Bone & Mineral Society and the Australian and New Zealand Bone and Mineral Society (ANZBMS) (Sydney, Australia)

“Menstrual irregularity is associated with higher bone mass in young women through alterations in endogenous androgen” (Poster presentation)

Travel grant awarded from ANZBMS

2009
Sharing Excellence in Research Conference. University of Tasmania (Hobart, Australia)

“Oral contraceptive use and bone mass in young women” (Oral presentation)

2010
The Australia and New Zealand Bone and Mineral Society (ANZBMS) 20th Annual Scientific Meeting (Adelaide, Australia)

“The association between oral contraceptive use, bone mass and fractures in both young and older women” (Oral presentation).

Travel grant awarded from ANZBMS

2010
Sharing Excellence in Research Conference. University of Tasmania (Hobart, Australia)

“Menstrual irregularity is associated with higher bone mass in young women which is mediated through alterations in endogenous androgen” (Poster presentation)
International Epidemiological Association (IEA) World Congress of Epidemiology (Edinburgh, Scotland)

“The association between oral contraceptive use and bone mass in both young and older women” (Poster presentation).

Travel grant awarded from the University of Tasmania
List of Abbreviations

ABS  Australia Bureau of Statistics
ACER  Australian Council for Education Research
ASHFS  Australian Schools Health and Fitness Survey
BMI  Body mass index
BUA  Broadband ultrasound attenuation
BMD  Bone mineral density
BMC  Bone mineral content
CATI  Computer assisted telephone interview
CDAH  Childhood Determinants of Adult Health study
CD  Changhi Ding
CI  Confident interval
CV  Coefficients of variation
DMPA  Depot medroxyprogesterone acetate
DXA  Dual-energy x-ray absorptiometry
EE  Ethinyl estradiol
ERT  Estrogen replacement therapy
FT  Free testosterone
FAI  Free androgen index
FFQ  Food frequency questionnaire
GIS  Geographical Information Systems
HRT  Hormone replacement therapy
ICC  Intra-class correlation coefficient
<table>
<thead>
<tr>
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<th>Description</th>
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<tr>
<td>IVF</td>
<td>In vitro fertilization</td>
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<tr>
<td>IPAQ</td>
<td>International physical activity questionnaire</td>
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<td>JSN</td>
<td>Joint space narrowing</td>
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<td>LTPA</td>
<td>Leisure time physical activity</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MET</td>
<td>Metabolic Equivalent Task</td>
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<tr>
<td>OC</td>
<td>Oral contraceptive</td>
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<td>OA</td>
<td>Osteoarthritis</td>
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<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PA</td>
<td>Physical activity</td>
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<td>PCOS</td>
<td>Polycystic ovary syndrome</td>
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<td>PCO</td>
<td>Polycystic ovaries</td>
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<td>PRR</td>
<td>Prevalence rate ratio</td>
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<td>QUS</td>
<td>Quantitative ultrasound</td>
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<td>QUI</td>
<td>Quantitative ultrasound index</td>
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<tr>
<td>RIA</td>
<td>Radioimmunoassay</td>
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<tr>
<td>SHBG</td>
<td>Sex hormone binding-globulin</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SDAC</td>
<td>Survey of Disability, Ageing and Cares</td>
</tr>
<tr>
<td>SF</td>
<td>Stella Foley</td>
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<tr>
<td>SOS</td>
<td>Speed of sound</td>
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<tr>
<td>TASOAC</td>
<td>Tasmanian Older Adult Cohort study</td>
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<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>WHR</td>
<td>Waist hip ratio</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>WOMAC</td>
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