Biomarkers in Osteoarthritis

by

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

(Medical Research)

University of Tasmania, November 2013

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	Doctor Danchi Jiang
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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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Statement of Co-Authorship

This thesis includes papers for which Oliver Stannus (OS) was not the sole author. OS was the lead in the research of each manuscript; however, he was assisted by the co-authors, whose contributions are detailed below.

Chapter 4:

Stannus O, Jones G, Quinn S, Cicuttini F, Dore D, Ding C. The association between leptin, interleukin-6 and hip radiographic osteoarthritis in older people: A cross-sectional study. Arthritis Research & Therapy. 2010;12(3): R95.

The contribution of each author:

> OS was responsible for data management and cleaning, carried out analysis and interpretation of data, prepared the initial manuscript draft and completed manuscript revisions.

> GJ and FC designed and carried out the study planning, participated in analysis and interpretation of data and critically revised the manuscript.

> QS participated in analysis and interpretation of data and critically revised the manuscript.

> DD critically revised the manuscript.

> CD designed and carried out the study planning, participated in analysis and interpretation of data, assisted with the initial manuscript draft and critically revised the manuscript.

Chapter 5:

Stannus O, Jones G, Cicuttini F, Parameswaran V, Quinn S, Burgess J, Ding C. Circulating levels of IL-6 and TNF-α are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Osteoarthritis Cartilage. 2010;18:1441-7.

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>
> QS participated in analysis and interpretation of data and critically revised the manuscript.
>
> VP and JB carried out data collection and critically revised the manuscript.
>
> CD designed and carried out the study planning, was responsible for data collection, participated in analysis and interpretation of data, assisted with the initial manuscript draft and critically revised the manuscript.

Chapter 6:

Stannus O, Jones G, Blizzard L, Cicuttini F, Ding C. Associations between serum levels of inflammatory markers and change in knee pain over 5 years in older adults: a prospective cohort study. Annals of the Rheumatic Diseases 2012 May 18. [Epub ahead of print]

The contribution of each author:

OS was responsible for data management and cleaning, carried out analysis and interpretation of data, prepared the initial manuscript draft and completed manuscript revisions.

GJ and FC designed and carried out the study planning, participated in analysis and interpretation of data and critically revised the manuscript.

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

CD designed and carried out the study planning, was responsible for data collection, participated in analysis and interpretation of data, assisted with the initial manuscript draft and critically revised the manuscript.

Chapter 7:

Carnes J, Stannus O, Cicuttini F, Ding C, Jones G. Knee Cartilage Defects in a Sample of Older Adults: Natural History, Clinical Significance and Factors Influencing Change over 2.9 years. Osteoarthritis and Cartilage 2012 Sep 6. [Epub ahead of print].

The contribution of each author:

OS and JC are co-first authors on this paper. They were responsible for data management and cleaning, carried out analysis and interpretation of data, prepared the initial manuscript draft and critically revised the manuscript.

CD designed and carried out the study planning, was responsible for data collection, participated in analysis and interpretation of data and critically revised the manuscript.

FC designed and carried out the study planning, participated in analysis and interpretation of data and critically revised the manuscript.

GJ designed and carried out the study planning, participated in analysis and interpretation of data, assisted with the initial manuscript draft, critically revised the manuscript and completed manuscript revisions.

Chapter 8:

Cross-sectional and longitudinal associations between circulating leptin and knee cartilage thickness in older adults. Stannus O, Cao Y, Jones G, Blizzard L, Antony B, Ding C. Manuscript submitted to Annals of the Rheumatic Diseases

The contribution of each author:

OS and YC are co-first authors on this paper. They carried out analysis and interpretation of data and prepared the initial manuscript draft. OS also collected the data for this paper and was responsible for data management and cleaning.

GJ designed and carried out the study planning, participated in analysis and interpretation of data and critically revised the manuscript.

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

BA critically revised the manuscript.

CD designed and carried out the study planning, participated in analysis and interpretation of data, assisted with the initial manuscript draft and critically revised the manuscript.

Chapter 9:

Stannus O, Jiang D, Cicuttini F, Cao Y, Ding C. Cartilage signal intensity on T1 weighted MRI: association with risk factors and measures of knee osteoarthritis. Manuscript submitted to Clinical Rheumatology.

The contribution of each author:

OS was responsible for data collection, data management and cleaning, carried out analysis and interpretation of data and prepared the initial manuscript draft.

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

FC designed and carried out the study planning, participated in analysis and interpretation of data and critically revised the manuscript.

YC critically revised the manuscript.

CD designed and carried out the study planning, participated in analysis and interpretation of data, assisted with the initial manuscript draft and critically revised the manuscript.

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Statement of Ethical Conduct

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.

Abstract

Osteoarthritis (OA) is a multifactorial disease of the joints, common among older adults, which can lead to pain, impaired function and reduced quality of life. This thesis aims to investigate the associations and predictive value of various hormonal, inflammatory and imaging biomarkers with OA outcomes in population-based studies of people with and without prevalent OA.

Two population samples were used in this thesis. The first group was a population-based sample of older adults aged 50-80 years (mean age: 62 years; 51% female). Followup measurements were conducted 2.7 (2.6-3.3) years later and again for questionnaire data 5.0 (5.3-6.8) years later. Magnetic resonance imaging (MRI) on the right knees was undertaken at baseline and first followup: knee cartilage volume, tibial bone area, cartilage defects and bone marrow lesions (BMLs) were measured or scored; cartilage mean T1 signal intensity and thickness were measured by semi-automated software. Baseline knee and hip x-rays were scored for joint space narrowing (JSN) and osteophytes. Serum leptin and cytokine levels were measured by immunoassay at baseline and first followup. Body morphometry was measured at baseline. Fat and lean mass measures were measured at baseline using dual-energy x-ray absorptiometry (DXA). Knee pain was assessed by questionnaires (WOMAC, Western Ontario and McMasters Osteoarthritis Index) at all timepoints.

The second group was a population-based sample of younger adults aged 26-51 (mean age 41; 64% female). Anthropometric, x-ray and MRI-derived scores and measures were obtained as in the first group. Urinary C-terminal crosslinking telopeptide of type II collagen (U-CTX-II) was measured by measured by immunoassay.

This thesis consists of 6 studies. In the first study, in older adults, circulating levels of both leptin and interleukin-6 (IL-6) were associated with hip JSN in both sexes and females respectively, independently of BMI. Adiposity was associated with hip JSN, but not after adjustment for leptin.

In the second study, baseline levels of both IL-6 and tumor necrosis factor alpha (TNF-α) were associated with medial tibiofemoral knee JSN. Baseline IL-6, change in IL-6 and change in TNF-α were associated with cartilage volume loss.

In the third study, in older adults, baseline or change over 2.9 years in circulating levels of high sensitivity C-reactive protein (hs-CRP), IL-6 and TNF-α were associated with change over 5 years in sub-scale or total WOMAC knee pain.

In the fourth study, higher leptin in older adults was significantly associated with lower femoral, tibial and patellar cartilage thickness. Fat measures were negatively associated with cartilage thickness, largely mediated by leptin. Baseline and change in leptin were associated with medial tibial cartilage thickness loss.

In the fifth study, knee cartilage defects in older adults were found to be common, not likely to regress, and to predict cartilage volume loss and risk of knee replacement.

In the final study, mean T1 MRI signal intensity of cartilage was negatively associated with BMI and same-region cartilage defects in younger and older adults; with U-CTX-II in younger adults; and with JSN and osteophytes in older adults at various sites. It predicted cartilage thickness loss over 2.7 years in older adults.

In conclusion, inflammatory and metabolic factors may play important roles in aetiology of cartilage loss and/or symptoms in OA. Cartilage defects predict cartilage loss and risk of knee replacement, and mean T1 MRI signal intensity of cartilage predicts loss of cartilage thickness. All these are potential biomarkers for OA at risk of development or progression, and thus possible targets for intervention.

Acknowledgements

I would like to begin by thanking my Primary Supervisor, Associate Professor Changhai Ding, to whom I owe the greatest debt of gratitude. Changhai has given up countless hours to ensure the smooth completion of my studies and has always been able to give me the support I have needed to carry out my research. I owe the success of my doctoral studies to the encouragement, patience and wisdom he has provided. I consider myself lucky to have had the opportunity to study under Changhai.

I would also like to thank Professor Graeme Jones, my co-supervisor and the head of the musculoskeletal unit at Menzies. Graeme's insights and advice have been key in shaping my research and bringing it to publication.

I also offer thanks to Dr Danchi Jiang for encouraging me to take the opportunity of pursuing a PhD. Continuing his support from my Honours degree to be a co-supervisor for my doctoral studies, Danchi has always made himself available to give advice and assistance, for which I am ever thankful.

I also thank Dr Stephen Quinn for his statistical expertise and many hours spent answering my questions. From my very first day at Menzies, Steve helped me to develop my skills in statistical analysis. His ready and practical assistance was crucial in generating and critiquing many of my results, as well as in responding to the requests of peer reviewers. I would also like to thank Associate Professor Leigh Blizzard for his extensive assistance. After Steve's departure, Leigh has made time for me in his busy schedule and ensured that I have continued to receive a high level of statistical support. I also would like to thank Leigh for providing me with the opportunity to work under him for the Australasian Epidemiological Association and for his support as a Graduate Research Coordinator.

Many thanks also to Professor Flavia Cicuttini, who has collaborated with me on many of my papers. Flavia's enthusiasm and team spirit have made her a delight to work with and her advice regarding my work has always been appreciated. I would also like to thank Associate Professor Yuelong Cao for his help with analysing and publishing results in two of my papers. I have been lucky to be able to collaborate with a researcher as hard-working and willing as Yuelong. I would also like to thank my other co-authors, Jonathan Carnes, Venkat Parameswaran and John Burgess for their contributions to our research.

I would like to thank all staff on both the TASOAC and Knee Cartilage Volume studies and give special thanks to the many participants and volunteers workers in these two studies, who have given their time and energy to make our research possible.

I would also like to acknowledge those sources of funding which were crucial in my research, being the University of Tasmania Rising Star Grant awarded to Professor Ding, which provided a stipend for me; and the financial supporters of the TASOAC and Knee Cartilage Volume studies, which were the National Health and Medical Research Council, the Tasmanian Community Fund, the Masonic Centenary Medical Research Foundation, the Royal Hobart Hospital Research Foundation, and the Arthritis Foundation of Australia.

I would also like to thank the ever-friendly Menzies staff, particularly Jodi Barling, Kay Nguo, Robert Warren, Petr Otahal, Stewart Wells and Kathy Thomson. I would like to give special thanks to the HealthIT staff, particularly Ben Duan and Alistair Chilcott, who have often given much-appreciated help with a variety of issues.

I give my heartfelt thanks to all my fellow students, past and present, for their friendship and for making the PhD experience at Menzies so much more enjoyable. In particular, I would like to thank Laura Laslett, Dawn Doré, Benny Antony, Tan Bui, Huynh Long Quan, Harbeer Ahedi, William Cuellar, Anitra Wilson, Jana Canary, Kara Martin, Michelle Callisaya, Peta Hitchens, Kylie Smith and Beverly Curry.

Special thanks to Jacqui, for your patience and loving support and through the long years of my PhD, for encouraging me when I have needed it, for listening to me, and for making sure life's not so tough. Further thanks to Rod and Meri for all your support.

My sincerest thanks to my family and friends for all the help and company during my PhD journey. Many thanks to my parents in particular, for always being there for me.

Publications Arising from the Thesis

Chapter 4: Stannus O, Jones G, Quinn S, Cicuttini F, Dore D, Ding C. The association between leptin, interleukin-6 and hip radiographic osteoarthritis in older people: A cross-sectional study. *Arthritis Research and Therapy. 2010;12(3): R95.*

Chapter 5: Stannus O, Jones G, Cicuttini F, Parameswaran V, Quinn S, Burgess J, Ding C. Circulating levels of IL-6 and TNF-α are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. *Osteoarthritis and Cartilage. 2010;18:1441-7.*

Chapter 6: Stannus O, Jones G, Blizzard L, Cicuttini F, Ding C. Associations between serum levels of inflammatory markers and change in knee pain over 5 years in older adults: a prospective cohort study. *Annals of the Rheumatic Diseases 2013; 72(4):535-40*

Chapter 7: Carnes J, Stannus O, Cicuttini F, Ding C, Jones G. Knee Cartilage Defects in a Sample of Older Adults: Natural History, Clinical Significance and Factors Influencing Change over 2.9 years. *Osteoarthritis and Cartilage 2012;20:1541-7.*

Chapter 8: Stannus O, Cao Y, Jones G, Blizzard L, Antony B, Ding C. Cross-sectional and longitudinal associations between circulating leptin and knee cartilage thickness in older adults. *Annals of the Rheumatic Diseases 2013 Sep 27 [e-pub ahead of print]*

Chapter 9: Stannus O, Jiang D, Cicuttini F, Cao Y, Ding C. Cartilage signal intensity on T1 weighted MRI: association with risk factors and measures of knee osteoarthritis. *Manuscript submitted to Clinical Rheumatology.*

Other Publications

Antony B, Jones G, Stannus O, Blizzard L, Ding C. Body fat predicts an increase and limb muscle strength predicts a decrease in leptin in older adults over 2.6 years. *Clinical Endocrinology 2012*. [Epub ahead of print]

Antony B, Ding C, Stannus O, Cicuttini F, Jones G. Association of baseline knee bone size, cartilage volume, and body mass index with knee cartilage loss over time: A longitudinal study in younger or middle-aged adults. *Journal of Rheumatology 2011; 38(9):1973-80*

Ding C, Stannus O, Cicuttini F, Antony B, Jones G. Body fat is associated with increased and lean mass with decreased knee cartilage loss in older adults: a prospective cohort study. *International Journal of Obesity 21 August 2012*. [Epub ahead of print]

Cao Y, Stannus O.P., Aitken D, Cicuttini F, Antony B, Jones G, Ding C. Cross-sectional and longitudinal associations between systemic, subchondral bone mineral density and knee cartilage thickness in older adults with or without radiographic osteoarthritis. *Annals of the Rheumatic Diseases July 2013*. [Epub ahead of print]

Scientific Presentations and Awards Arising from the Thesis

2009   Australian Rheumatology Association and New Zealand Rheumatology
Association Combined Annual Scientific Meeting
*Circulating levels of IL-6 and TNF-α are associated with knee radiographic
osteoarthritis and knee cartilage loss in older adults*
Wellington, New Zealand
(**Oral presentation**)

2009   World Congress on Osteoarthritis (Osteoarthritis Research Society International
Annual Meeting)
*Serum levels of inflammatory markers, knee radiographic osteoarthritis, and knee
cartilage loss in older adults*
Montreal, Canada
(Oral presentation - presented by co-author)

2009   World Congress on Osteoarthritis (Osteoarthritis Research Society International
Annual Meeting)
*The associations between leptin, interleukin-6 and hip radiographic osteoarthritis
in older people*
Montreal, Canada
(Oral presentation - presented by co-author)

2011   Australian Rheumatology Association Annual Scientific Meeting
*Cartilage signal intensity on MRI: association with body mass index, cartilage
defects and type II collagen breakdown*
Brisbane, Australia
(Poster presentation - **Best basic science poster prize**)

2011   World Congress on Osteoarthritis (Osteoarthritis Research Society International
Annual Meeting)
*Inflammatory biomarkers are predictive of increases in knee pain over 5 years in
older adults*
San Diego, USA

2011 Australian Rheumatology Association Annual Scientific Meeting
Inflammatory biomarkers are predictive of increases in knee pain over 5 years in older adults
Brisbane, Australia
(Poster presentation)

2011 Osteoarthritis Research Society International Imaging Meeting
Cartilage signal intensity on MRI: association with body mass index, cartilage defects and type II collagen breakdown
Salzburg, Austria.
(Poster presentation)

2012 American College of Rheumatology Annual Meeting
Cross-sectional and longitudinal associations between circulating leptin and knee cartilage thickness in older adults
Washington DC, USA
(**Oral presentation** - presented by co-author)

List of Abbreviations

2D	two-dimensional
BIPED	burden, investigative, prognostic, efficacy or diagnostic
BLOKS	Boston–Leeds osteoarthritis score
BME	bone marrow edema
BMI	body mass index
BML	bone marrow lesion
CI	confidence interval
COMP	cartilage oligomeric protein
CRP	C-reactive protein
CTX-II	C-terminal crosslinking telopeptide of type II collagen
CV	coefficient of variation
DALY	disability-adjusted life year
dGEMRIC	delayed gadolinium-enhanced MRI of cartilage
DMOAD	disease modifying anti-osteoarthritis drug
DXA	dual energy x-ray absorpiometry
FSE	fast spin echo
GEE	generalised estimating equation
GRE	gradient recall echo
HOAMS	hip osteoarthritis MRI scoring system
hs-CRP	high-sensitivity C-reactive protein
IFN-γ	interferon gamma
IL-1	interleukin 1
IL1-β	interleukin 1-beta
IL-6	interleukin 6
JSN	joint space narrowing
KCVS	knee cartilage volume study
KL	Kellgren–Lawrence
KOSS	knee osteoarthritis scoring system
MMP	matrix-metalloproteinase
MOAKS	MRI knee osteoarthritis score
MRI	magnetic resonance imaging
NO	nitric oxide

NOS	nitric oxide synthase
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
OARSI	osteoarthritis research society international
OHA-MRI	Oslo hand osteoarthritis MRI score
OP	osteophyte
QALY	quality-adjusted life year
RA	rheumatoid arthritis
ROA	radiographic osteoarthritis
ROI	region of interest
SD	standard deviation
TASOAC	Tasmanian older adult cohort
THR	total hip replacement
TJR	total joint replacement
TKR	total knee replacement
TNF-α	tumor necrosis factor alpha
uCTX-II	urinary C-terminal crosslinking telopeptide of type II collagen
WHR	waist–hip ratio
WOMAC	Western Ontario and McMasters pain questionnaire
WORMS	whole organ magnetic resonance imaging score

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