

THE ROLE OF ZINC IN CHRONIC DISEASE

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Declaration

The 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 the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968.

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Thesis by publication statements

I hereby certify that this thesis is submitted in the form of a series of publications of which I am first author. I have included as part of the thesis a written statement from each co-author; and endorsed by the Deputy Head of Faculty (Research), attesting to my contribution to the joint publications.

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List of publications

1. **Khanrin Phungamla Vashum**, Mark McEvoy, Abul Hasnat Milton, Md. Rafiqul Islam, Stephen Hancock and John Attia. **Is Serum Zinc Associated with Pancreatic Beta Cell Function and Insulin Sensitivity in Pre-Diabetic and Normal Individuals? Findings from the Hunter Community Study.** *PLOS One* January 08, 2014 (DOI: 10.1371/journal.pone.0083944)
2. **Khanrin Phungamla Vashum**, Mark McEvoy, Zumin Shi, Abul Hasnat Milton, Md. Rafiqul Islam, David Sibbritt, Amanda Patterson, Julie Byles, Deborah Loxton and John Attia. **Is dietary zinc protective for Type 2 diabetes? Results from the Australian Longitudinal Study on Women's Health.** *BMC Endocrine Disorders* 2013, **13**:40 (DOI: 10.1186/1472-6823-13-40)
3. **Khanrin Phungamla Vashum**, Mark McEvoy, Abul Hasnat Milton, Patrick McElduff, Alexis Hure, Julie Byles and John Attia. **Dietary zinc is associated with a lower incidence of depression: findings from two Australian cohorts.** *Journal of Affective Disorders* 166 (2014) 249–257 (DOI: 10.1016/j.jad.2014.05.016)
4. **Khanrin Phungamla Vashum**, Mark McEvoy, Abul Hasnat Milton, Patrick McElduff, Alexis Hure, Julie Byles and John Attia. **Is dietary zinc associated with a higher incidence of cardiovascular disease: findings from two Australian cohorts.** Submitted to the 'Nutrition, Metabolism & Cardiovascular Diseases' for publication.

List of additional publications with relevance to this thesis

1. Md. Rafiqul Islam, Iqbal Arslan, John Attia, Mark McEvoy, Patrick McElduff, Ariful Basher, Waliur Rahman, Roseanne Peel, Ayesha Akhter, Shahnaz Akter, **Khanrin P Vashum** and Abul Hasnat Milton. **Is serum zinc level associated with prediabetes and diabetes? A cross-sectional study from Bangladesh.** *PLOS One* April 17, 2013 (DOI: 10.1371/journal.pone.0061776)

2. Jun Shi Lai, Annette Moxey, Gabriel Nowak, **Khanrin Vashum**, Kylie Bailey, Mark McEvoy, **The Efficacy of Zinc Supplementation as Therapy for Depression: Systematic review of randomized controlled trials.** *Journal of Affective Disorders.* (DOI: 10.1016/j.jad.2011.06.022)

Statement of Contribution of Authors

We the undersigned co-authors attest that the research higher degree candidate **Khanrin Phungamla Vashum** contributed to conceptualization of the idea, study design, analyzed and interpreted the data, and developed all of manuscript included in this 'thesis by publication'.

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Synopsis

This thesis by publication is composed of a background, rationale & aims, brief literature review, four papers, and a final chapter providing conclusions. All but one of the papers relates to prospectively investigating the role of dietary zinc in chronic disease, which has been examined inadequately in the literature. At this stage of the thesis, three of the four papers have been accepted for publication in peer-reviewed journals. The final paper has been currently submitted to a peer-reviewed journal that is internationally recognised.

Chapter 1 outlines the background, structure of the thesis and describes the rationale and aims of this research.

Chapter 2 provides a summary of the general literature on the current understanding of the role of zinc in normal human physiology and chronic disease in particular. This chapter does not review literature specific to each health outcome investigated, which is presented and discussed in each of the chapters dealing with these health outcomes.

Chapter 3 (Paper 1), “Is Serum Zinc Associated with Pancreatic Beta Cell Function and Insulin Sensitivity in Pre-Diabetic and Normal Individuals? Findings from the Hunter Community Study” reports the association between serum zinc concentration and Homeostasis Model Assessment (HOMA) parameters cross-sectionally in a random sample of 452 older community-dwelling men and women in Newcastle, NSW, Australia. HOMA parameters were found to be significantly different between normoglycaemic and prediabetes groups ($p < 0.001$). In adjusted linear regression, higher serum zinc concentration was associated with increased insulin sensitivity ($p = 0.01$) in the prediabetic group and a significant association between smoking and worse insulin sensitivity was also observed. This paper has been published in PLOS ONE.

Chapter 4 (Paper 2), “Is dietary zinc protective for type 2 diabetes? Results from the Australian longitudinal study on women’s health,” reports the longitudinal association of dietary zinc with incident type 2 diabetes in 8921 women, aged 50-55 years at baseline over 6-years of follow-up. 333 incident cases of type 2 diabetes were identified at the end of follow-up and after adjustment for dietary and non-dietary factors, the

highest quintile of dietary zinc intake had almost half the odds of developing type 2 diabetes (OR = 0.50, 95% C.I. 0.32–0.77) compared with the lowest quintile. Similar findings were observed for the zinc/iron ratio; the highest quintile had half the odds of developing type 2 diabetes (OR = 0.50, 95% C.I. 0.30–0.83) after adjustment of covariates. This paper has been published in BMC Endocrine Disorders.

Chapter 5 (Paper 3), “Dietary zinc is associated with a lower incidence of depression: Findings from two Australian cohorts” reports the longitudinal association of dietary zinc with incident depression in two large Australian cohort aged 50 and above over 6-years of follow-up. Both studies showed that low dietary zinc intake is associated with a greater incidence of depression in both men and women, after adjusting for potential confounders. Compared to those with the lowest zinc intake, those with the highest zinc intake had significantly lower odds of developing depression with a reduction of about 30–50%. This paper has been published in Journal of Affective Disorders.

Chapter 6 (Paper 4), “Prospective Study of Dietary Zinc Intake and Risk of Cardiovascular Disease in Women,” reports the longitudinal association of dietary zinc and cardiovascular disease (CVD) over 6-years of follow-up in a cohort of women aged 50–55 years at baseline. The study showed that risk of CVD increases with increased intake of dietary zinc. Compared to those in the lowest quintile of zinc intake those with in the highest quintile of zinc intake had significantly higher odds of developing CVD (OR= 1.67, 95% CI 1.08, 2.62) at the end of the follow-up. The same finding was also observed between energy-adjusted zinc to iron ratio and risk of developing CVD.

This has been submitted to the ‘Nutrition, Metabolism & Cardiovascular Diseases’ journal in July 2014.

Conclusions (Chapter 7). This program of research provided formative assessment of the potential role of dietary zinc in the following chronic diseases: Type 2 diabetes, depression and cardiovascular diseases. Given that this thesis studies were carried out in an Australian population, additional prospective cohort studies in other populations are needed to support the causal relationship between dietary zinc and these health outcomes. Hence, research that employs a longitudinal design, and rigorous

randomized controlled trials aimed at determining the efficacy of zinc in the prevention of chronic disease are needed. Furthermore, studies looking into the precise role and mechanisms for the effects of zinc compared to other essential nutrients from diet are needed to establish and reinforce the importance of dietary zinc in this chronic disease and other diseased state.