THE ROLE OF L-ARGININE AND METHYLATED-ARGININES IN HEALTH AND 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.

________________________________________
Mark McEvoy        Date
Statement of Collaboration

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

Mark McEvoy
Date
Statement of Authorship (thesis by publication)

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 the thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

Mark McEvoy

Date
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Synopsis
This thesis by publication is composed of a background, rationale & aims, brief literature review, five papers, and a final chapter providing conclusions. All but one of the papers relate to exploring the role of L-arginine and the endogenous nitric oxide synthesis inhibitors, known as methylarginines, in a number of health and disease outcomes not previously examined in the literature. At the time of submission, four of the five papers have been accepted for publication in peer reviewed journals. The final paper is currently under peer review in an internationally recognised journal.

Chapter 1 outlines the structure of the thesis and describes the rationale and aims of this research. It also describes the candidate’s contribution to this research as well as the candidate’s contribution to the design and conduct of the larger parent cohort study from which the data was derived.

Chapter 2 provides a summary of the general literature relevant to methylarginines; the role of asymmetric dimethylarginine (ADMA) in health and disease in particular. This chapter does not review literature specific to each health outcome investigated – this is presented and discussed in each of the chapters dealing with these health outcomes.

Chapter 3 (Paper 1) is a description of the methods used for the conduct of the Hunter Community Study, the larger cohort study from which the data for each methylarginine sub-study was derived. This paper has been published in the International Journal of Epidemiology.

Chapter 4 (Paper 2), “Memory impairment is associated with serum methylarginines in older adults”, reports the cross-sectional association between serum concentrations of L-arginine and the methylarginines, ADMA and symmetric dimethylarginine (SDMA), with subjective and objective memory impairment in sample of 483 community-dwelling older Australian adults. Multivariate analysis revealed that SDMA and diabetes were significantly associated with objective memory impairment (Adjusted Odd ratio (AOR) = 3.90; 95% CI. 1.21 – 12.52 for fourth quartile (Q4) of
ADMA, SDMA, education, number of general practitioner visits and atrial fibrillation were all statistically significantly associated with **subjective** memory impairment. (AOR = 1.82; 95% CI. 1.04 – 3.18 for Q4 ADMA). This paper has been published in Current Alzheimer’s Research.

**Chapter 5 (Paper 3),** “Serum methylarginines and spirometry-measured lung function in older adults”, reports the cross-sectional association between serum concentrations of L-arginine and the methylarginines, ADMA and SDMA, with spirometric lung function measures (Forced Expiratory Volume in 1 sec. (FEV1), Forced Vital Capacity (FVC), FEV1/FVC) in sample of 483 community-dwelling older Australian adults. In unadjusted analyses, ADMA and L-arginine/ADMA ratio were both statistically significantly associated with FEV1, FVC, and FEV1/FVC. These associations were attenuated but remained largely significant for ADMA and L-arginine/ADMA ratio with FEV1 and FVC with adjustment for a wide range of potential confounders. In none of the analyses was SDMA associated with any measures of spirometric lung function. This paper has been published in PLOS ONE.

**Chapter 6 (Paper 4),** “Serum methylarginines and incident depression in a cohort of older adults”, reports the longitudinal association between serum concentrations of L-arginine and the methylarginines, ADMA and SDMA, with incident depression in a sample of 483 community-dwelling older Australian adults over 6-years of follow-up. In adjusted analyses ADMA, SDMA, L-arginine, gender, and asthma remained statistically significant predictors of incident depression at follow-up. Quartile 3 of ADMA concentration was associated with 3.5 times the odds of developing depression compared with Q1 (OR = 3.54; 95% CI. 1.25 – 9.99). This paper has been published in Journal of Affective Disorders.

**Chapter 7 (Paper 5),** “The role of L-arginine and endogenous methylarginines in irritable bowel syndrome”, reports the results of nested case-control study that examined serum concentrations of L-arginine and the methylarginines, ADMA and SDMA, with incident irritable bowel syndrome in community-dwelling older Australian adults. Cases of irritable bowel syndrome, defined according to Rome III
criteria (N=156), and controls (N=332) were identified from within the cohort at the 5-year follow-up. In adjusted logistic regression analyses, L-arginine, ADMA, SDMA, L-arginine/ADMA ratio, and Kessler-10 psychological distress scores, were statistically significant, independent predictors of irritable bowel syndrome. Higher serum L-arginine concentration had the largest effect on irritable bowel syndrome diagnosis with the odds of IBS in those with serum L-arginine at the 75th (84 µmol/L) versus 25th (46 µmol/L) percentile of 9.03 (95% CI: 5.99-13.62). L-arginine had the best discriminative ability with a bias-adjusted area under the receiver operator characteristic curve of 0.859. This paper is currently under peer review in the journal GUT.

Conclusions (chapter 8). This program of research provided formative assessment of the potential role of L-arginine and endogenous methylarginines in the following NO-dependent health outcomes: cognition, depression, lung function, and the functional gastrointestinal disorder, irritable bowel syndrome. Given that this research mostly utilized exploratory cross-sectional or case-control designs to examine the potential role of L-arginine and methylarginines in these health outcomes, further research is needed to support a causal relationship. Hence, future research designs that employ longitudinal analyses and rigorous randomised controlled trials aimed at determining the effects of modifying L-arginine and/or methylarginine levels are needed to establish if these molecules are markers or mediators of disease within the nervous, respiratory, and gastrointestinal systems.