AN ANALYSIS OF HIGHER PROTEIN DIETS ON RENAL FUNCTION

A COMPARISON OF HIGHER VERSUS LOWER DIETARY PROTEIN INTAKE ON GLOMERULAR FILTRATION RATE IN HEALTHY ADULTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

By ARJUN SITHAMPARAPILLAI, H.B.Sc.(Kin)

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Masters of Science in Global Health

McMaster University MASTER OF SCIENCE IN GLOBAL HEALTH (2015) Hamilton, Ontario

TITLE: A Comparison of Higher versus Lower Dietary Protein Intake on Glomerular Filtration Rate in Healthy Adults: A Systematic Review and Meta-Analysis AUTHOR: Arjun Sithamparapillai, H.B.Sc.(Kin) (McMaster University) SUPERVISOR: Professor S.M. Phillips NUMBER OF PAGES: ix, 69

LAY ABSTRACT

Globally, the leading causes of mortality in industrialized countries are cardiovascular disease (CVD), stroke, and type 2 diabetes (T2D). Deaths from these chronic diseases now outpace deaths due to malnutrition. Being overweight and obese increases the risk of both morbidity and mortality from CVD, stroke, and T2D. Global rates of overweight and obesity have now reached 'epidemic' proportions and the World Health Organization has stated that, "… [a] global epidemic of overweight and obesity – 'globesity' – is taking over many parts of the world. If immediate action is not taken, millions will suffer from an array of serious health disorders." Over the past 20-30 years, the popularity of higher protein energy restricted diets have grown due to the potential benefits regarding weight loss, appetite regulation, and maintenance of lean (muscle) mass. Additionally, the expansion of the global 'middle-class' has resulted in families allocating more income towards meat products as a primary protein source in their diet. A health concern is that higher protein intake may have an adverse effect on kidney function. In individuals with chronic kidney disease, higher protein diets have been shown to result in further renal impairment. However, the effects of increased protein intake in healthy populations are unclear. The aim of this systematic review and meta-analysis was to compare higher versus lower protein diets on kidney function in healthy populations based on the literature to date. This was accomplished by looking at changes in glomerular filtration rate (the rate at which kidneys filter blood), which is the 'gold standard' marker of kidney function.

ABSTRACT

Background: Higher protein diets, especially from animal sources, have seen a rise in popularity due to potential metabolic. This may have consequences for kidney function particularly in rising middle class populations who are allocating more income towards meat. The objective of this systematic review and meta-analysis was to evaluate the effects of higher versus lower protein intake on glomerular filtration rate (GFR) in adult populations without renal impairment.

Methods: Search strategies were developed and electronic databases searched: MEDLINE and EMBASE. Data were extracted up until June 3, 2015. The main outcome measure was GFR and a random effect model (Cochrane's Review Manager Version 5.3) was used to pool mean differences in GFR values.

Results: Database searches yielded 25 trials from 1914 articles that were eligible for analysis based on inclusion/exclusion criteria. 12 studies were randomized controlled trials and 11 studies were crossover trials. As a result of data presented, 2 crossover studies were treated as 4 trials to result in 25 total trials. A total of 810 subjects from 25 trials were included in this systematic review and meta-analyses. The age of participants was 24-62 years and their BMI was 21-36 kg/m^2. Higher protein compared to lower protein-containing diets were associated with increased GFR values [mean difference (MD): 8.33 ml/min (95% CI 4.87 to 11.79), $P < 0.00001$] but this was less pronounced when assessing change from baseline GFR values [MD: 4.71 ml/min (95% CI 0.06 to 9.36), $P = 0.05$]. Moreover, significant heterogeneity was present and funnel plot asymmetry indicated potential publication bias in both meta-analyses.

Conclusion: Higher protein diets were associated with increased GFR, however, these results were inconclusive due to significant heterogeneity and overestimation by random effect analyses. There is still no clear evidence that high protein diets negatively impact renal function in healthy populations.

ACKNOWLEDGEMENTS

I would like to take this moment to extend my utmost appreciation for all the support provided by my supervisor, Dr. Stuart M. Phillips. He assisted me along the way and ensured that I was always on the right path to achieve all my goals and checkpoints in every circumstance. I would also like to thank my committee for providing me with amazing support: Ms. Laura Banfield for always being there no matter what time of day to help solve any problem in this process, and Dr. Scott Brimble for providing a plethora of knowledge on nephrology and being so patient. A special thank you goes to Dr. Michaela Devries-Aboud for helping me throughout this entire new research experience. Finally, I would like to thank my family. Amma, Appa, Aravind, Mikayla and Arun, you are always there for me in every walk of life. Last of my family but certainly not least, is my beloved wife Rachel. You are the reason I have gotten to where I am today and you are my daily inspiration as you keep me grounded in God; He is the one whom I am most thankful to above all.

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS AND SYMBOLS

AMDR: Acceptable Macronutrient Distribution Ranges

BMI: Body Mass Index

CC: Creatinine Clearance

CDC: Center for Disease Control and Prevention

CKD: Chronic Kidney Disease

CKD-Epi: Chronic Kidney Disease Epidemiology Collaboration

DRI: Dietary Reference Intake

eGFR: Estimated Glomerular Filtration Rate

FAO: Food and Agriculture Organization

GFR: Glomerular Filtration Rate

iGFR: Inulin Glomerular Filtration Rate

MDRD: Modification of Diet in Renal Disease

n.d.: No Data

RCTs: Randomized Controlled Trials

RDA: Recommended Dietary Allowance

RMR: Resting Metabolic Rate

SDΔ: Change Standard Deviation

TEC: Total Energy Consumption

UNU: United Nations University

WHO: World Health Organization

DECLARATION OF ACADEMIC ACHIEVEMENT

Conceived and designed the experiments: AS, SP, MD, LB, SB

Performed the experiments: AS

Analyzed the data: AS

Contributed reagents/materials/analysis tools: AS, LB, MD

Contributed to the writing of the manuscript: AS, SP

Stuart M. Phillips Ph.D., FACSM, FACN
Professor, Department of Kinesiology, McMaster University
Exercise Metabolism Research Group – Protein Metabolism Research Lab
Physical Activity Centre for Excellence (PACE) Researcher

Laura Banfield MLIS., MHSc.
Health Sciences Librarian, McMaster University
Assistant Clinical Professor, School of Nursing
Liaison for School of Nursing, Midwifery Education, and Global Health Program

Scott Brimble, MD, MSc., FRCP(C)
Associate Professor of Medicine, McMaster University
Divisional Director, Nephrology
Provincial Medical Lead - Early Detection and Prevention of Progression, Ontario Renal Network

Michaela Devries-Aboud Ph.D., MSc., BSc.
Post-doctoral Fellow, McMaster University

INTRODUCTION

The past 20-30 years have witnessed a rise in the amount of attention given to hypoenergetic diets to lose weight. Attempts have been made to ascertain the role in diet-induced weight loss of numerous nutrients, differing food groups, macronutrient proportions, and individual foods and food products. One macronutrient in particular that has seen an increase in attention is that of dietary protein (Kasiske, Lakatua, Ma, & Louis, 1998). Coming from a variety of sources including plants and meat, protein has been an integral part of the human diet for centuries. Current guidelines are to consume protein at the Recommended Dietary Allowance (RDA) of 0.8 g protein/kg/d or within the Acceptable Macronutrient Distribution Range of 10-35% of an individual's daily energy requirement (USDA & DHHS, 2010). Our need for protein arises due to a daily turnover of proteins in our body. Proteins are degraded and synthesized simultaneously, but their constituent building blocks, amino acids, are often metabolized and the metabolic waste products excreted. The obligatory loss of nitrogen (arising from the catabolism of amino acids), the essential nuclide of protein, is mostly in the form of urea. Since there is a daily loss of nitrogen, this in essence means a loss of protein and thus we have a need to consume protein to replace these losses.

Proteins are composed of 20 different amino acids, 9 of which are considered to be essential while the remaining 11 are non-essential. Non-essential amino acids are deemed as such due to our ability to endogenously synthesize and utilize these amino acids through biochemical pathways without having to ingest them (Jackson, 1983).

Since the synthesis of new proteins requires all 20 amino acids, essential amino acids must be consumed as part of our diet as they cannot be produced via metabolic pathways from other amino acids or metabolites. Plant and animal sources of protein both contain amino acids but the protein quality (i.e., content of the essential amino acids) between foods can vary immensely. A protein-containing food is identified as 'complete' if it contains all nine of the essential amino acids. The quality of a protein is a product of the content of essential amino acids, the level of those amino acids, and how digestible the protein is (Food and Agriculture Organization of the United Nations, 2013). Many animal-source proteins such as meats and dairy products contain complete sources of protein and are highly digestible and so are considered 'high quality' proteins (Hoffman & Falvo, 2004). However, plant source-proteins can be incomplete, or at least lower quality, sources of protein that are lacking in one or another essential amino acid and often are much less digestible due to the presence of anti-nutritional compounds such as dietary fibre. Therefore, diets in which protein is obtained predominantly (or exclusively) through the consumption of grains and vegetables necessitates consumption of foods in pairs of legume-based (beans) and grain-based (rice or corn) foods that are complimentary in terms of their essential amino acid content (Young & Pellett, 1994).

The human body contains a variety of tissues and organs that are comprised of proteins containing all 20 amino acids, thus dietary protein intake is a necessary aspect of daily living. Sufficient protein consumption enables adequate growth and development, appropriate functioning of the immune system, neurotransmitter synthesis, enzyme function, hormonal production, and protein synthesis (Friedman, 2004; Huff & Carroll,

1980). The daily loss of amino acids (degraded and excreted as urinary urea), means that we need to ingest protein to fulfill these roles throughout all stages of human life. However, differences between populations in terms of needs and values have resulted in diverse global patterns of protein consumption. Populations that experience a rise in rates of obesity typically see an absolute increase in the amount of protein consumed. Nonetheless, many hypoenergetic diets aiming to promote weight loss to address obesity and weight gain often advocate for a relative increase in the consumption of protein as a proportion of dietary energy (Wycherley, Moran, Clifton, Noakes, & Brinkworth, 2012). A brief evaluation of the current obesity pandemic and accompanying global patterns of protein consumption will provide a further understanding of why the study of the effects of dietary protein on human health is worthwhile.

Obesity, Globalization, and Meat Consumption

While there are a myriad of contributing factors (genetics, geography, mental health, age, sex, socioeconomic status), weight gain in humans is fundamentally the result of energy intake surpassing energy expenditure over time (Ravussin et al., 1988). This concept is not new, but the rapidity with which populations have experienced increasing obesity rates, and the corresponding increase in global awareness of this problem, is a relatively recent phenomenon. When an individual is overweight or obese they have excess body fat that increases the risk of developing various health impairments and certain chronic diseases (WHO, 2015). This is a major problem as obesity is associated with significantly greater morbidity and all-cause mortality worldwide when compared to populations of normal weight (Flegal, Kit, Orpana, & Graubard, 2013).

The most commonly used method of defining and measuring overweight and obesity is the body mass index (BMI), which is calculated by dividing an individual's height in metres by their weight in kilograms squared. Although the BMI does not directly measure fat composition, it allows for a quick compilation and comparison of overweight and obesity internationally. A BMI from 25-29.9 classifies a person as overweight and a BMI over 30 classifies an individual as obese (CDC, 2012). According to the World Health Organization (WHO), Obesity rates have more than doubled since 1980; on a global basis, 39% of adults over age 18 were overweight in 2014, and 13% were obese (WHO, 2015). In addition, most of the world's population now lives in countries where overweight and obesity kills more people than underweight (i.e., due to malnourishment). In 2012, it was estimated that a total of 1.9 billion adults were overweight and in the previous year a staggering 42 million children under the age of five were either overweight or obese (WHO, 2015). Underscoring the importance of obesity is the fact that more deaths worldwide, for the first time in human history, are now linked to overweight and obesity as opposed to malnourishment (WHO, 2015). Furthermore, this obesity pandemic is not a problem solely of developed nations with higher household incomes; a large and growing group of developing countries now face what has been termed a double burden of disease (Marshall, 2004). In impoverished communities, the problem of childhood and adult undernutrition remains a concern, but populations in both upper and lower socioeconomic classes within the same nation will also experience a rise in obesity and its related comorbidities (Marshall, 2004). Excess energy consumption had predominantly remained a concern in more industrialized North American, Australian,

and European nations, but obesity has also grown to be a large problem in South America, Africa, and Asia (Tee, 2002; Uauy, Albala, & Kain, 2001). Countries such as India and China, where the usual 'industrialized' BMI classification underestimate risk due to a racial dependence in risk at each BMI level (Chen et al., 2013; Misra & Khurana, 2009), continue to combat malnutrition in rural areas and slums, yet have an increased number of obesity-related cases of hypertension and diabetes in urban areas (Popkin, Horton, Kim, Mahal, & Shuigao, 2001). Similarly, Brazil and Argentina are just two South American nations that are experiencing accelerated healthcare costs due to obesity and have had to introduce necessary health policy reform projects (Arbex, Rocha, Aizenberg, & Ciruzzi, 2014).

The factors influencing the rise in overweight and obesity around the world are numerous, but a number of lines of evidence point to increasing globalization as a driving force amidst the various stimuli. The concept of globalization and what it entails could be an entirely distinct discussion, however, in the context of this thesis the increased consumption of food energy and dietary protein that has accompanied the current obesity pandemic is of interest. Specifically, a brief evaluation of the globalization of meat and dairy products as foods and international consumption patterns further confirms the necessity of an analysis of dietary protein intake on human health. The consumption of these protein sources is recognized and often encouraged in countries with food insecurities due to environmental factors, war, in people with lower socioeconomic status, or due to geographic challenges to receiving adequate food supply (Kennedy, Nantel, & Shetty, 2004; Varadharajan, Thomas, & Kurpad, 2013). Nonetheless, in

developed nations, where food security is less of an issue, the top dietary protein source is usually some form of meat (WHO, n.d.).

A trend seen with several definitions of globalization is the emergence of global markets (Al-Rodhan & Stoudmann, 2006). In general, to varying degrees of extent, globalization is a by-product, or cause, of global economies and markets (Al-Rodhan & Stoudmann, 2006). Concepts of the world being a global 'shopping mall' have been made, with notions of ideas and products being constantly available worldwide (Kanter, 2003). Thus, globalization can be summarized as the increased mobility of goods, services, and ideas throughout the world. Globalization's impact has been evident with meat products as the past few decades have witnessed increased global production and availability of livestock-derived produce, while consumption has increased correspondingly (WHO, n.d.). The rise in the global consumption of meat may be explained in part by cultural ideas and values surrounding meat as a 'reward' of economic prosperity. For example, in China the rise in the average worker's take home pay has directly paralleled the rise in consumption of meat, a previously unaffordable food (B. Hoffman, 2014).

Historically, livestock and related produce were both produced and consumed locally, yet this is a pattern that has changed even in the last 20 years (Lambin & Meyfroidt, 2011). Local production and consumption of meat is all that was possible before the ability to transport large quantities of the commodity over large distances was possible. As technology progressed and countries became more industrialized, the trading

of goods over distances of all sizes multiplied extensively (Gilpin & Gilpin, 2000). This has been witnessed in particular with meat and dairy products. These high biological value protein sources have been experiencing increased consumption and demand over the past century, but as noted this has been exponentially accelerated in more recent decades (WHO, n.d.).

The United States of America, a highly developed nation and prominent global trader of goods, consumed over 60 kg of meat per capita-year in the 1960s (WHO, n.d.). This was only up from approximately 56 kg per capita-year in 1909 (Barnard, 2010). Such a trend was largely predictable since the most influential factor attributing to increased consumption from 1909 to 1960 was population. However, consumption of meat and milk from the 1960's to 2000 and projection of meat consumption in 2030 illustrates a disproportionate growth in demand for these products. Globally, an average person's meat consumption rose by 50% from 24 kg to 36 kg per capita-year from the 1960s to 1999 (Bruinsma, 2003). Industrialized nations showed the largest increases in consumption from 62 kg to 88 kg per person. Notwithstanding, developing countries followed suit by increasing their meat consumption from 10 kg to 26 kg per capita-year (WHO, n.d.). A near doubling of meat consumption was seen in Near East and North Africa and significant increases were also seen in Latin America and the Caribbean (WHO, n.d.). The largest increase in meat consumption was an increase from 9 kg to 38 kg per capita-year in East Asia (WHO, n.d.). Projected meat consumption in 2030 predict global consumption to increase to 45 kg per capita-year, with developing countries increasing to 37 kg per capita-year, East Asia increasing to 58 kg per capita-year and

industrialized countries reaching close to 100 kg per capita-year (WHO, n.d.). Though not as substantial, increases have also been seen in milk consumption over the past half century. Average global consumption of milk only increased from 74 kg to 78 kg per capita per year, but significant increases were still seen around the world (WHO, n.d.). Developing nations saw increases from 28 kg to 45 kg, Latin American and Caribbean milk consumption rose from 80kg to 110kg, milk consumption in South Asia rose from 37 kg to 67 kg, and industrialized countries reported an increase in consumption from 186 kg to 212 kg per capita-year (WHO, n.d.).

A large part of the increases seen in livestock consumption can be accounted for by population growth, however, per capita consumption has increased and supply systems have improved resulting in access to meat that was not previously available. Thus, trends in meat consumption are meeting demand from consumers, even with increasing populations and with no indication of declining. According to the available statistics this is a global trend and not one restricted to developed nations. One contribution to this trend is the allocation of funds when an impoverished family experiences a rise in income level (Delgado, 2003). As developing countries experience population growth and urbanization, families that reap the benefit of this tend to spend more income on animal products than previously (Delgado, 2003). Thus, the ‘reward’ for national and personal economic prosperity is an increased consumption of meat. This can be explained by the sociocultural values surrounding meat intake around the world and this is crucial to consider. If the global demand for meat – just one source of dietary protein – continues to increase the effect it may have on human physiology warrants thorough investigation.

The social value of meat is recognized globally in various contexts and provides some explanations for why the demand for meat is increasing. In many countries, meat is prized as a prestigious symbol and in several cultures it remains the focal point of a luxurious or celebratory dinner. In Uganda, a family's worth of plantain bananas may be traded for a much smaller supply of chicken, while in indigenous Indonesian culture meat is exchanged at funerals with the symbolism of status and honour (Fiddes, 2004). Similar values around meat are seen in Brazil where beef is highly praised and production is rising (Ribeiro & Corcao, 2013). Additionally, in Brazil and other nations, references to European colonization and influence are frequently made (Ribeiro & Coraco, 2013). As illustrated by Kerr and Charles (1986), British families viewed meat as the most important part of the main meal of the day and 'proper' meals would always contain some form of meat. The same emphasis on meat was seen in war-time, as both the German and American military placed importance on the value of protein or high-fat beef respectively, whether rationed or not (Fiddes, 2004). Globalization and the transfer of goods and ideas have evidently played a role in the increasing consumption and production of meat. The demand and supply of livestock has consistently risen with the population and ever-growing middle class of developing countries (Senauer & Goetz, 2003). The sociocultural value of meat has always been present but has now transcended both local and national social boundaries (Al-Rodhan & Stoudmann, 2006; Ribeiro & Corcao, 2013). It is estimated that per-capita food energy intake has increased in the last 50 years and this is now an almost global trend (Kennedy et al., 2004; Traill, Mazzocchi, Shankar, & Hallam, 2014). Thus, as energy intake rises so too has protein intake in both

absolute and relative amounts and it is crucial to evaluate the effect this might have on human health. However, an important point to consider is that a large body of evidence also points to the potential of dietary protein to aid in countering some of the adverse health effects of obesity (Layman et al., 2015; Leidy et al., 2015).

Dietary Protein Consumption: A Global Player in the Obesity Pandemic?

It is evident that sustained greater energy consumption in excess of energy expenditure will result in weight gain, mostly in the form of body fat. Numerous studies point toward the potential for improved metabolic function with increases in relative protein intake [for reviews see (Leidy et al., 2015; Wycherley, Moran, et al., 2012)]. It is estimated that less than one third of the world population has a primarily meat-based (not including fish) diet and as such the majority of the world's protein is consumed through plant sources (Grigg, 1996; Pimentel & Pimentel, 2003). Thus, the need to evaluate elevated protein intake of all sources on human physiology is necessary, particularly if protein intake is glorified from a sociocultural aspect as well as evidence-based literature.

The current recommended dietary allowance (RDA) for dietary protein intake in North America is 0.8 g/kg body weight/day, which is part of the dietary reference intakes (DRI) that guide nutrient intake recommendations. The World Health Organization, United Nations University (UNU), and Food and Agriculture Organization of the United Nations (FAO) have set the recommended intake for protein at the same level (Joint WHO/FAO/UNU Expert Consultation, 2007). Several national governments follow this guideline. While the RDA is a level of dietary protein that is generally considered safe

and allows for adequate growth and development, as well as physiological functioning, there are a number of studies that point to the possibility of increasing protein beyond the minimal level to an 'optimal' level that may be accompanied by better health (Wolfe & Miller, 2008). There are reports that advocate for the potential benefits of increased dietary protein intake in adults who are elderly (Paddon-Jones et al., 2015), adults who want to lose weight or regulate appetite (Leidy et al., 2015), and adults who are athletes or highly active persons (Phillips, 2012).

A recent evidence-based recommendation for protein intake in the elderly was completed in 2013 (Bauer et al., 2013). This international study group re-evaluated protein requirements in the elderly as a result of three common factors influencing loss of muscle mass and functionality with aging: a basic inadequate intake of protein, a reduced ability to use available protein (i.e., loss of the normal anabolic response to protein to build new proteins), and a greater need for protein due to disease (Bauer et al., 2013). More specific needs in the elderly include sarcopenia (lean mass loss with aging) and osteoporosis (Gaffney-Stomberg, Insogna, Rodriguez, & Kerstetter, 2009). The review by Bauer et al. (2013) concluded that the recommended protein intake for healthy adults over the age of 65 should be at least 1.0-1.2 grams protein/kg/d if not more based on individual circumstances. Similar results have been found with several dietary interventions evaluating the effects of increased protein intake on lean mass sustenance (Borst, 2004; Gaffney-Stomberg et al., 2009), many of which were accounted for in the review by Bauer et al. (2013).

Research has also illustrated a benefit of increased protein intake in healthy adults who are trying to lose weight (Layman, 2004; Wycherley, Brinkworth, Clifton, & Noakes, 2012). The benefit in both groups revolves around maintenance of lean mass, better regulation of appetite, and an increased thermogenic effect of protein consumption. Increased lean mass (i.e., skeletal muscle) is crucial in all populations as it improves the ability to perform activities of daily living, it decreases risk of falls and fractures, and it increases resting metabolic rate (RMR) (Baumgartner et al., 2004; Szulc, Beck, Marchand, & Delmas, 2005). The maintenance of RMR is the most crucial given the current obesity pandemic; as individuals try to lose weight a great percentage of this weight loss may be the loss of lean mass (Frestedt, Zenk, Kuskowski, Ward, & Bastian, 2008). Since lean mass, outside of the liver, is a large contributor to RMR (Müller, Wang, Heymsfield, Schautz, & Bosy-Westphal, 2013), a loss of lean mass can often be an influential factor of resulting weight gain when dieters return to their original lifestyle (Wadden, Foster, Stunkard, & Conill, 1996). In populations that are attempting to lose weight, studies have shown the ability to preserve lean mass when dieting or exercising with an increase in the amount of caloric consumption that is coming from protein (Frestedt et al., 2008; Josse, Atkinson, Tarnopolsky, & Phillips, 2011).

Evidence-based reviews provide arguments for the increase of dietary protein intake in healthy adults from the prevention of obesity point of view considering its potential effects on weight loss and lean mass preservation (Krieger, Sitren, Daniels, & Langkamp-Henken, 2006; Wycherley, Moran, et al., 2012). This has been the stance taken by a number of energy-restricted diets that have arisen over the past decades. In the

context of this review, it is evident that dietary protein intake is increasing globally regardless of whether from dietary or socioeconomic reasoning, with no signs of declining given the accompanying sociocultural influences. Therefore, an evaluation of increased dietary protein intake on human health is necessary. An often-cited reason for why higher dietary protein may be disadvantageous, even in the context of weight loss, is the impact of such a diet on renal function. This concern arises despite statements from within the WHO report on protein intakes.

> The Joint WHO/FAO/UNU Expert Consultation (2007) report states: There is clear evidence that high intakes of protein by patients with renal disease contribute to the deterioration of kidney function… However, the suggestion that the decline of glomerular filtration rate that occurs with advancing age in healthy subjects… can be attenuated by reducing the protein in the diet appears to have no foundation. (p. 224)

> Additionally, the DRI report from the Institute of Medicine (Lupton, 2005) stated: Restriction of dietary protein intake is known to lessen the symptoms of chronic renal insufficiency… This raises two related, but distinct questions: Do high protein diets have some role in the development of chronic renal failure? Do high protein intakes accelerate the progression of chronic renal failure? The concept that protein restriction might delay the deterioration of the kidney with age was based on studies in rats in which low energy or low protein diets attenuated the development of chronic renal failure… [however] this mechanism is unlikely to

> operate in humans. In particular, the decline in kidney function in the rat is mostly due to glomerulosclerosis, whereas in humans it is due mostly to a decline in filtration by nonsclerotic nephrons… These factors point to the conclusion that the protein content of the diet is not responsible for the progressive decline in kidney function with age. (p. 842)

Thus, two of the most widely read and followed dietary guidelines agree that a decline in renal function with age is not due to increased dietary protein content.

High Dietary Protein Intake and Renal Function in Adults

Kidneys are two small 'bean-shaped' organs in the human body that filter the entire blood supply multiple times a day through the functional unit of the organ, the nephron (NIH, 2014). At the beginning of the nephrons are glomerular capillaries. When blood enters the glomerulus, water and solutes (including the three primary protein-related solutes: urea, amino acids, and ammonia) are filtered through the walls of the capillaries before the fluid receives further filtration and is then reabsorbed or excreted. It is during the preliminary filtration stage that protein and blood cells, which are not filtered, are concentrated (Venkatachalam & Rennke, 1978). Neither protein nor cells pass through the selectively permeable glomerular capillary membrane unless the glomerular membrane is damaged. Therefore, the concentration of proteins increases along the glomerular capillaries as blood plasma is continuously filtered. This buildup of proteins will result in an increase in oncotic pressure in the glomerular capillaries, which then increases the resistance to filtration. This is a brief and very cursory description of

glomerular filtration – the filtration of fluid out of the glomerular capillaries – and the crucial influence that dietary protein has on the concentration gradient (Venkatachalam & Rennke, 1978). Both glomerular filtration and urinary protein concentrations are individually used to evaluate kidney function. Proteinuria is typically not supposed to occur in a healthy kidney and at certain levels it indicates malfunctioning at the glomerular capillary level (Jafar et al., 2003). Protein leaking into the Bowman's capsule can result in excess fluid being filtered out of the capillaries as well as the loss of important proteins that are not meant to be excreted. Additionally, the rate at which glomerular filtration (the glomerular filtration rate – GFR) occurs can offer valuable information about whether the kidneys are operating at maximum efficiency or not. The evaluation of kidney function has led to the development of guidelines for individuals living with chronic kidney disease (CKD) specifically with how they should modify their diet to reduced solute load (e.g. consume less sodium). However, corollary logic as opposed to evidence-based analysis has often resulted in precautions being advocated for in adult populations with healthy renal function including the lowering of dietary protein intake. Before evaluating high protein intake on healthy adults, a brief description of glomerular filtration measurements and CKD will provide foundation for the basis of the negative associations between high protein intake and kidney function.

Glomerular filtration rate (GFR) measures the rate at which fluid passes through the glomeruli and this is widely considered to be the best measure of kidney function (Stevens, Coresh, Greene, & Levey, 2006). Currently, a number of different methods exist to measure GFR in an individual, all involving the clearance of a certain indicator.

The gold standard for measuring GFR is inulin clearance since inulin is a safe filterable substance that cannot be metabolized (Delanaye et al., 2012). Inulin clearance was utilized more in the past, however, there has been a drift away from the use of this index of renal function as inulin is expensive, not readily available, and requires inconvenient processes to use appropriately. Other exogenous markers used to measure GFR include iohexol, iothalamate, and various isotopes. The most common method of measuring GFR is creatinine clearance (CC) since creatinine exists naturally in the human body as a breakdown product of creatine, which is stored primarily in skeletal muscle (Delanaye et al., 2012). The kidneys act to keep levels of creatinine in the body fairly consistent, however, limitations with CC exist due to inconsistencies based on dietary influences, other human factors affecting levels of creatinine, and evidence exists to suggest that CC overestimates GFR (Delanaye et al., 2012; Levey et al., 1999). Therefore, equations have been derived to estimate GFR that account for individual differences and features such as: the Cockcroft-Gault formula, the Modification of Diet in Renal Disease (MDRD) study equation, and the Chronic Kidney Disease Epidemiology (CKD-Epi) Collaboration equation (Michels et al., 2010). All of these formulas still require and utilize CC as their outcome measure, but adjust for factors such as age, sex, and race.

The measure of GFR is in mL/min/1.73 m^2 and a normal value for adults with healthy kidneys is over 90 (Levey et al., 2011). GFR tends to decline with age as well as with decreasing efficiency of the kidneys. When GFR drops below 90 the risk for chronic kidney disease (CKD) is increased, however, the disease is defined by stages (Levey et al., 2011). An individual is at increased risk of CKD if they have a family history of

CKD, diabetes, high blood pressure, or other risk factors alongside a GFR above 90. Stage 1 CKD refers to a GFR above 90 in an individual with kidney damage. Stage 2 CKD is classified by a GFR of 60-89 and corresponds with kidney damage and mild loss of renal function. Stage 3a involves mild to moderate loss of kidney function and a GFR of 44-59 while stage 3b corresponds with moderate to severe loss of kidney function and a GFR of 30-44. Stage 4 CKD occurs when an individual's GFR is between 15 and 29 as this indicates a severe loss of kidney function. Stage 5 CKD signifies renal failure and is classified by a GFR of less than 15 (Levey et al., 2011).

The effects of dietary protein intake have been studied on individuals living with CKD and typically there is advocacy for lower protein diets in persons with confirmed CKD. A systematic review by Fouque & Aparicio (2007) outlined 11 reasons why limiting protein intake is beneficial in individuals living with CKD, one of which was the increased GFR associated with increased protein intake. The "Brenner hypothesis" suggests that chronic hyperfiltration associated with increased protein intake may lead to renal disease in the long term (Brenner, Meyer, & Hostetter, 1982), and this is amplified in individuals with CKD as the nephrons lose the ability to effectively filter all the solute waste produced from protein metabolism. Additionally, a threshold of safe protein intake is suggested as 0.6-0.8 g of protein/kg of body weight/day. Adding to this evidence was a Cochrane review 2 years later that found reducing protein intake in patients with CKD reduced the incidence of renal death by 32% when compared to higher or unrestricted protein diets (Fouque & Laville, 2009). The results of these reviews and other RCTs have highlighted the concern with increased protein intake in populations with CKD, but this

knowledge has been, some would argue inappropriately, carried over into recommendations for healthy populations; a conclusion that is not supported by the results of clinical trials.

Increased dietary protein intake may exacerbate the effects of CKD, but the negative effects on kidney function in healthy populations may not exist and remains inconclusive. While the notion of increased GFR in healthy populations potentially contributing to future renal disease is consistently debated, the foundation of this argument originated from a paper published over 30 years ago which speculated this concept (Brenner et al., 1982). Further literature evaluating the effects of high protein intake in healthy populations exists, but systematic reviews evaluating renal function in these individuals are few and far between. Moreover, no meta-analyses to date have evaluated the change from baseline GFR and mean differences in study populations. Thus, a systematic review and meta-analysis of the literature on high protein intake and GFR will provide clarity on this matter. Given the evidence laid out in the introductory portion of this thesis, I propose it is prudent to conduct a systematic review and meta-analysis to ascertain the impact of higher dietary protein on renal function in healthy persons.

METHODS

Search Strategy and Study Identification

A systematic search of published studies was conducted in MEDLINE (from year 1946) and EMBASE (from year 1974) inclusive to June 3rd, 2015. Search terms included dietary proteins, amino acids (essential and non-essential), protein-restricted diet, vegetarian diet, fish protein, vegetable protein, milk, yolk, eggs, soy protein, protein metabolism, nitrogen metabolism, high protein diet, low protein diet, glomerular filtration rate, inulin clearance, kidney circulation, renal circulation, kidney function, kidney circulation, proteinuria, albuminuria, creatinine, inulin, and hemoglobinuria. Searches were limited to clinical trials using the maximizing sensitivity McMaster Health Information Research Unit (HIRU) filters (Patel, Rogers, & Haux, 2001; Wilczynski & Haynes, 2002). Searches could not utilize the limitation to humans provided by the databases as these filters were found to result in missed studies as a result of improper indexing of several studies. Humans were referred to as subjects, participants, adults, patients, and more yet were not all indexed appropriately. Thus, searches were limited to humans via filtering out mice and rats (the two most common animal models on which similarly-related physiology/dietary research was being undertaken). Lastly, searches were limited to the English language and duplications were removed.

Study Inclusion/Exclusion Criteria

Studies were included if they were randomized control trials (RCT) or crossover studies that studied the effect of higher dietary protein intake versus moderate (greater than the

RDA, but lower than the higher protein intake) or lower protein (RDA or less) intake on glomerular filtration rate in adults aged 18 years or older. Studies were excluded if they enrolled participants with type one diabetes, CKD, and any other pre-existing indicators of renal impairment (i.e. proteinuria, microalbuminuria, macroalbuminuria, prior stone formation). Adults had to be in otherwise good health and conditions including obesity, hypertension, and type two diabetes were permitted in this review. Studies were excluded if adults had just undergone any surgical or operative interventions. Inclusion criteria for diet allowed protein to be in the form of food, powder, or tablets as long as all sources of protein were consumed orally. Studies were excluded if the high protein diet for subjects was not a minimum of one of the following daily requirements: at least 1.5 grams of protein per kilogram of bodyweight, at least 20% of total caloric intake coming from protein, or at least 100 g of protein per day. Additionally, the lower protein diet had to be at least 5% less, as a percentage of total daily energy intake, coming from protein when compared to the high protein diet (Santesso et al., 2012). Dietary interventions were measured in weeks and had to be at least 1 week long (rounding up if diets lasted between 4 and 6 days). Studies were excluded if diets were 3 days or less or if the study was acute and studied only one meal or protein load. All of the following calculations or estimations of glomerular filtration rate were permitted: creatinine clearance, isotope clearance, inulin clearance, iothalamate clearance, iohexol clearance, sinistrin clearance, Cockgroft-Gault calculations, Modification of Diet in Renal Disease (MDRD) calculations, and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculations. Additionally, if GFR values were stated in units other than mL/min, then appropriate conversions were

made to standardize all values. Finally, studies were excluded if they were only provided in abstract form.

Included Studies, Data Extraction and Data Syntheses

The MEDLINE search yielded a total of 1241 hits and the EMBASE search yielded a total of 668 hits after all duplicates were removed within each database. After all 1909 abstracts were examined, 27 studies were selected for full text review. Four studies were excluded due to either only being published in abstract form or the inability to obtain the full study. Five studies were excluded upon reviewing the full articles, therefore a remaining total of 18 studies were included in the analyses. Previous systematic reviews and reference lists were also examined and this process acquired a further five articles that brought the total number of included studies to 23. A flow chart of the study inclusion process is displayed in Figure Appendix 1.

The following data was extracted from each study: the first author's last name, year of publication, study design, total number of subjects, percentage of female subjects, number of diabetic subjects within each group, sample size of each group, the age distribution (in years) and BMI of all subjects, the duration of the diets (in weeks), predominant sources of dietary protein, the total energy content (TEC) of diets, daily protein intake (as absolute weight in grams, relative weight as g/kg of bodyweight, or as a percentage of TEC), the method used to evaluate GFR and eGFR, and GFR measures (in mL/min) at baseline and post dietary intervention. All subject baseline data and outcome measures were equated to identical values when presented in different units, and inputted

into RevMan 5 (Review Manager Version 5.3, The Cochrane Collaboration 2015). If data was missing then the authors were contacted or values were extracted from given tables and graphs. If data still remained as missing and values could not be inferred from the publication, then these studies were excluded from the respective comparison or analysis. Mean differences and change standard deviation (SDΔ) were also calculated and inputted. Mean differences for each group within a study (high protein and low protein) were calculated as:

$$\text{Mean difference} = \text{Mean post} - \text{Mean pre}$$

SDΔ was inputted from reported values where possible. When SDΔ was not reported and raw data was not available, SDΔ was calculated as:

$$SD\Delta = \sqrt{[(SDpre)2 + (SDpost)2 - 2 \times corr\ (pre,post) \times SDpre \times SDpost]}$$

where corr (pre,post) is the correlation between pre and post values across participants. This was calculated from studies that reported SDΔ and/or raw data for a given outcome and applied across trials as detailed in the Cochrane Handbook for Systematic Reviews of Interventions (The Cochrane Collaboration, 2011). If a study reported mean differences and standard deviations for two different populations (due to age or another demographic) then they were treated as separate studies in the data analysis. Additionally, if a crossover study utilized three different diets for its subject group, then the data for the highest protein and lowest protein diets were used in the meta-analysis to allow for adequate difference in dietary protein intake.

Two meta-analyses were performed on GFR, the outcome of interest. One meta-analysis compared the mean differences across studies and as such provided an assessment of the change from baseline values experienced by each diet (change from baseline GFR means). The second meta-analysis evaluated the difference in post values (post GFR means) and encompassed all studies as some experiments did not provide enough data to acquire the SD of mean differences (and therefore could not be included in the previous meta-analysis). Weighted mean differences and differences in post values were analyzed using fixed- or random-effects meta-analyses. Forest plots were generated for each outcome to demonstrate study-specific effect sizes and their corresponding 95% confidence intervals (CIs) as well as the overall pooled effect.

All data extracted to RevMan 5 was assessed for heterogeneity and publication bias. Heterogeneity was tested using Chi^2 and I^2 tests. Significance was set as $P < 0.01$for the Chi^2 test and I^2 values > 75% were considered to illustrate significant heterogeneity. In the presence of heterogeneity, random effects meta-analysis was utilized. If heterogeneity was absent then fixed meta-analysis was used. Publication bias was assessed with visual inspection of funnel plots. Lastly, when funnel plot asymmetry existed in the presence of heterogeneity then the results from both fixed- and random-effects models were compared to verify that random effects estimate did not confirm the high protein diet as more influential on GFR increase (Sterne et al., 2011).

RESULTS

Study and Subject Characteristics

23 trials from 1914 articles met the inclusion criteria and were not excluded based on exclusion criteria. The detailed progression of study inclusion is presented in Appendix 1. Additionally, all the study and subject characteristics that were extracted from the studies, as well as pre and post GFR data, are listed in Table 1. The year of publication for all included studies ranged from 1975 to 2013. All of the studies were randomized controlled trials or crossover studies; 12 studies were RCTs and 11 studies were crossover trials. A total of 810 subjects from 23 trials were included in this systematic review and meta-analyses. The age of participants ranged from 24.1 years to 62.4 years and the BMI of participants ranged from 21.2 to 36.1. To allow for ease of reference, the studies cited in the remainder of this results section refer to the number of the study in Table 1. Three studies did not report a mean age but rather a range in itself (7, 9, 12). Additionally, 5 studies did not report a mean BMI (1, 7, 12, 13, 16). In 2 studies (21/22, 23/24) the data was provided for the younger and older age groups exclusively, thus the results were treated as two different studies for accurate input purposes (and hereon are treated as individual trials). Moreover, 2 crossover studies (4, 10) provided the subjects with three different dietary treatments over the course of the trial, therefore the lowest and highest protein treatments were utilized in data analyses to allow for the greatest difference in dietary protein intake. With regards to gender, 4 studies were restricted to male participants (4, 5, 12, 25) and 5 studies were restricted to female participants (7, 11, 14,

17, 19). In each of the remaining trials, female subjects represented 25-90% of the total participants. 3 of the included studies were restricted solely to individuals living with type two diabetes (13, 15, 18). All trials involved participants living without chronic kidney disease or any other renal impairment.

Diet Protocol Characteristics

The duration of all dietary interventions ranged from 1 week to 104 weeks. 23 of the 25 trials had participants undergo a high protein and/or a low protein diet for the length of the intervention. In the remaining 2 crossover trials, all participants underwent a high protein, lower protein and lowest protein diet (4, 10). With the exception of 5 studies (2, 6, 18, 23, 24), some or all information about the major sources of dietary protein was provided for all diets . 3 studies did not provide any information about the major sources of dietary protein for all diets (2, 23, 24), and 2 studies did not provide any information for the lower protein diet sources (6, 18). Of the 22 trials that reported sources of dietary protein in one or all of the subject groups, all studies incorporated animal sources of protein except 2 (8, 18) which limited protein intake to vegetable and/or wheat sources. The total energy consumption (TEC) in kcal/day varied for all the trials but included isocaloric diets, ad libitum diets, and caloric restriction diets. Only 1 trial did not report information about the caloric intake of the participants (10). Data for dietary protein intake was provided in various formats, but all high protein diets met a minimum of one of the following daily requirements: at least 1.5 grams of protein per kilogram of

bodyweight, at least 20% of total caloric intake resulting from protein, or at least 100 grams of protein per day.

GFR Measurements and Outcomes

The GFR methods used as well as the pre and post GFR values are listed in Table 1. Throughout the 25 different trials, a number of different GFR measurements were utilized. 6 studies used inulin clearance or some other form of isotope clearance (1, 5, 18, 20, 23, 24), 5 studies used the Modification of Diet in Renal Disease study calculation (3, 14, 15, 21, 22), 1 study used the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation (10), 2 studies did not provide the methods used to obtain GFR (11, 13), and the remaining 11 studies used unadjusted measures of creatinine clearance. All 25 trials provided GFR post values and were included in the meta-analysis evaluating the effect of diets at the end of the interventions. However, only 14 trials provided both pre and post GFR values and were able to be included in the meta-analysis of mean differences. The SDΔ was provided in 6 of the 14 trials (2, 9, 11, 14, 15, 25) so the average correlation coefficient was calculated from these given values to determine SDΔ for the remaining 8 trials. The mean differences and SDΔ are listed in Appendix 2 by the first author of study and publication year.

The pooled estimates of effect size (95% confidence intervals) are illustrated in Figure 1 and Figure 2 for the effects of high protein versus low protein diets on GFR. When looking at all post GFR means, high protein diets were associated with significantly higher GFR increases when compared to low protein diets [MD: 8.33

ml/min (95% CI 4.87 to 11.79), P < 0.00001]. When assessing change from baseline GFR means within each diet, high protein diets were again associated with significantly higher GFR increases when compared to low protein diets, but by almost 50% less than the previous analysis [MD: 4.71 ml/min (95% CI 0.06 to 9.36), P = 0.05].

Publication Bias and Heterogeneity

The funnel plots illustrated in Figure 3 and Figure 4 were visually inspected for publication bias. Little to moderate asymmetry was observed for both post GFR mean differences (Figure 3) as well as change from baseline GFR mean differences (Figure 4), however Figure 3 less resembled the typical inverted funnel shape when compared to Figure 4. Based on these evaluations there may be the potential for publication bias. Substantial heterogeneity (P < 0.01) was also found in both analyses. For post GFR mean differences, I^2 = 80% and for change from baseline GFR mean differences I^2 = 95%. This significant heterogeneity may have arisen from the extensive variation in study characteristics as diet, length of intervention, BMI, age, existing health conditions, and GFR measurements were not standardized amongst all studies. However, due to the presence of both heterogeneity and asymmetry in funnel plots, a comparison of fixed-effect and random-effects meta-analyses was performed. Results showed that random-effects meta-analysis was greater in both evaluations, thus caution should be taken when interpreting the results of these analyses and determining that high protein intake is associated with an increase in GFR.

Table 1. Characteristics of the included studies in the meta-analyses and GFR measurements.

#[a]	Design[b]	Group	Sample			Age[c]	BMI[d]	Time[e]	Protein Sources	Protein Intake[f]	Energy Intake[g]	GFR/eGFR Method[h]	GFR Pre[i]		GFR Post[i]	
			Total (N)	% Female	Diabetic (N)								Mean	SD	Mean	SD
1	Cross	Higher	8	50	0	26.5	-	1	Milk, cheese, meat, fish	2g/kg, 23%	Isocaloric	Inulin Clearance	-	-	112.7	12.1
		Lower			0			1	Tablets containing amino acids	0.3g/kg, 3%	Isocaloric	Inulin Clearance	-	-	100.1	14.4
2	RCT	Higher	43	72	0	50.2	34	68	-	30%	1552 for 12 weeks, 1982 for 4 weeks	Creatinine Clearance	100.2	55.4	124.2	50.7
		Lower			0			68	-	15%	1552 for 12 weeks, 1982 for 4 weeks	Creatinine Clearance	101.8	32.5	112.6	35.7
3	RCT	Higher	68	63	0	51.5	33.6	52	125 mL full-fat milk, 70 g full-fat cheddar cheese, 1 medium (50-55g) egg, 100g (cooked weight) ham, tuna, beef, chicken, turkey, 40g raw unsalted nuts	35%	1433-1672	MDRD	90	17	91.2	17.8
		Lower			0			52	300mL non-fat milk, 20g reduced-fat cheese (2x per week), 150g (raw weight) beef, chicken, pork, lamb (5x per week), 150g fish (1x per week), 100g	24%	1433-1672	MDRD	83.8	13.8	83.6	11.8

#[a]	Design[b]	Group	Sample			Age[c]	BMI[d]	Time[e]	Protein Sources	Protein Intake[f]	Energy Intake[g]	GFR/eGFR Method[h]	GFR Pre[i]		GFR Post[i]	
			Total (N)	% Female	Diabetic (N)								Mean	SD	Mean	SD
									beans/lentils (2x per week), 200g non-fat yogurt (3x per week), 20g raw unsalted nuts, 50g tinned fish (3x per week)							
4	Cross	Higher	6	0	0	24.7	21.2	2	Low protein rusk, low protein spaghetti, all white turkey, low fat ground beef	150g/day	Isocaloric	Creatinine Clearance	-	-	122	15.1
		Lower			0			2	Low protein rusk, low protein spaghetti, all white turkey, low fat ground beef	75g/day	Isocaloric	Creatinine Clearance	-	-	105	14.4
		Lowest			0			2	Low protein rusk	5.6g/day	Isocaloric	Creatinine Clearance	-	-	98	15.6
5	Cross	Higher	24	0	0	24.1	22.3	1	Animal sources (including milk and milk products) and plant sources	2.4g/kg, 26.6%, 181g/day	2743	Sinistrin Clearance	-	-	141	8
		Lower			0			1	Animal sources (including milk and milk products) and plant sources	1.2g/kg, 13.3%, 88g/day	2743	Sinistrin Clearance	-	-	125	5
6	RCT	Higher	307	68	0	45.5	36.1	104	Unlimited protein consumption according to guidelines from Dr. Atkins' New Diet Revolution	Unlimited	Ad libitum	Creatinine Clearance (calculated by dividing urinary creatinine excretion (mg/d) by 1440 (min/day) and then dividing again by the serum creatinine (mg/dl) x100)	135	35.3	138.7	35.3
		Lower			0			104	-	15%	1200-	Creatinine	133	41.8	129.5	41.8

#[a]	Design[b]	Group	Sample			Age[c]	BMI[d]	Time[e]	Protein Sources	Protein Intake[f]	Energy Intake[g]	GFR/eGFR Method[h]	GFR Pre[i]		GFR Post[i]	
			Total (N)	% Female	Diabetic (N)								Mean	SD	Mean	SD
											1500 (Female), 1500-1800 (Male)	Clearance (calculated by dividing urinary creatinine excretion (mg/d) by 1440 (min/day) and then dividing again by the serum creatinine (mg/dl) x100)				
7	RCT	Higher	6	100	0	23-28	-	9	100g Lean ground beef, Bread contained: 20g Casein, 20 g lactalbumin, 30 g wheat gluten and 25 g dehydrated egg white	123g/day	2290	Creatinine Clearance	-	-	102.8	5.1
		Lower			0			9	100g lean ground beef, vegetables	46g/day	2290	Creatinine Clearance	-	-	90.6	2.7
8	Cross	Higher	20	25	0	55.6	26	4	80g wheat gluten protein bread, vegetable protein	27.40%	2764	Creatinine Clearance	-	-	110	31.3
		Lower			0			4	Vegetable protein	15.60%	2835	Creatinine Clearance	-	-	104	35.8
9	RCT	Higher	16	90	0	19-54	28.9	6	Egg beater scramble with ham and cheese, 3 cups skim milk, 1.5 cups bean and pasta soup, 3 oz. open-faced turkey and provolone (1oz) sandwich, chicken chow mien dinner	31.5%, 134g/day	1700	Creatinine Clearance	103.8	24.9	85.3	24.6
		Lower			0			6	1 oz. cream cheese, 2 cups skim milk, 1 cup bean and pasta soup, chicken	15%, 64g/day	1700	Creatinine Clearance	82	16.5	84.5	22.1

#[a]	Design[b]	Group	Sample			Age[c]	BMI[d]	Time[e]	Protein Sources	Protein Intake[f]	Energy Intake[g]	GFR/eGFR Method[h]	GFR Pre[i]		GFR Post[i]	
			Total (N)	% Female	Diabetic (N)								Mean	SD	Mean	SD
									chow mien dinner							
10	Cross	Higher	156	45	0	53.5	30.2	6	48% Plant Protein	25%	-	CKD-epi Cystatin C Equation	92	16.3	95.81	8.1
		Lower			0			6	36% Plant Protein	15%	-	CKD-epi Cystatin C Equation	92	16.3	91.23	7.9
		Lowest			0			6	36% Plant Protein	15%	-	CKD-epi Cystatin C Equation	92	16.3	91.57	9.6
11	Cross	Higher	7	100	0	26	23	1	Poultry, fish, egg-whites, meat and dairy sources	2.1g/kg, 134.9g/day	2009-2147	-	103.8	13.2	116.1	22
		Lower			0			1	Meat and dairy sources	0.7g/kg, 45.8g/day	2138-2446	-	98	11.9	101.8	10.3
12	Cross	Higher	6	0	0	21-29	-	1.5	100g Lean ground beef, 32.5g Casein, 25g lactalbumin, 37.5g wheat gluten, vegetable sources	142g/day	3000	Creatinine Clearance	-	-	116	7
		Lower			0			1.5	100g Lean ground beef, Vegetable sources	47g/day	3000	Creatinine Clearance	-	-	105	10
13	RCT	Higher	99	52	53	59.4	27-40	52	Lean meat, chicken and fish	30%	1529	-	70.2	11.9	73.4	17.6
		Lower			46			52	Lean meat, chicken and fish	15%	1529	-	72.6	15.2	74.58	17.6
14	RCT	Higher	46	100	0	50	30.6	12	180g cooked pork, loin, ham, or Canadian bacon (40% of protein from pork)	30%	Normal diet – 750	MDRD	86	9.16	84	9.16
		Lower			0			12	Milk products (13% of protein from milk)	18%	Normal diet – 750	MDRD	74	13.8	78	10
15	RCT	Higher	42	55	21	62.4	33.3	12	Soy-based foods (e. g. tofu), milk products, fish and poultry	30%	1272	MDRD	70.8	15	73.8	13.9
		Lower			21			12	Evidence-based nutrition	15%	1272	MDRD	65.5	14.5	68.5	18.9

#[a]	Design[b]	Group	Sample			Age[c]	BMI[d]	Time[e]	Protein Sources	Protein Intake[f]	Energy Intake[g]	GFR/eGFR Method[h]	GFR Pre[i]		GFR Post[i]	
			Total (N)	% Female	Diabetic (N)								Mean	SD	Mean	SD
									recommendations for the treatment and prevention of diabetes mellitus							
16	RCT	Higher	30	60	0	20-65	27-40	16	Lean meat, poultry, and low-fat dairy foods	40%	Isocaloric	Creatinine clearance (calculated by: [(urine creatinine concentration in mmol/L) x (urine volume in mL/1140 min)/(plasma creatinine concentration in (mol/L) · 1000 mL 1 · min 1)] x 0.7)	121	37.4	141	44.9
		Lower			0			16	Lean meat, poultry, higher-fat milk, and oil and nuts high in monounsaturated fat	20%	Isocaloric	Creatinine clearance (calculated by: [(urine creatinine concentration in mmol/L) x (urine volume in mL/1140 min)/(plasma creatinine concentration in (mol/L) · 1000 mL 1 · min 1)] x 0.7)	117	52	124	60
17	RCT	Higher	98	100	0	49.5	32.5	12	250mL low fat milk, 200g low-fat yogurt, 300g lean meat, poultry or fish	34%	1269	Creatinine Clearance	82.3	23.3	76.7	20.5
		Lower			0			12	250mL low fat milk, 80g lean meat, poultry or fish	7%	1247	Creatinine Clearance	81.9	22.9	72.9	21.5
18	Cross	Higher	10	33	10	58	33	3	Casein, gelatine, vegetable proteins, yeast,	2g/kg, 22%	2175	Isotope Clearance (99mTechnicium-DTPA	118.2	28.2	118.8	38.4

#[a]	Design[b]	Group	Sample			Age[c]	BMI[d]	Time[e]	Protein Sources	Protein Intake[f]	Energy Intake[g]	GFR/eGFR Method[h]	GFR Pre[i]		GFR Post[i]	
			Total (N)	% Female	Diabetic (N)								Mean	SD	Mean	SD
									and soy			(diethylenetriamine pentaacetic acid) plasma clearance)				
		Lower			10			3	-	0.8g/kg, 10%	2103	Isotope Clearance (99mTechnicium-DTPA (diethylenetriamine pentaacetic acid) plasma clearance)	130.8	46.2	92.4	48
19	Cross	Higher	15	100	0	60.5	26.5	8	Pork, turkey breast, beef round, ham, chicken breast	20%	2296	Creatinine clearance (calculated from serum and urinary creatinine, which were measured using alkaline picric acid)	-	-	82.8	10.8
		Lower			0			8	Vegetable sources	12%	2296	Creatinine clearance (calculated from serum and urinary creatinine, which were measured using alkaline picric acid)	-	-	72.6	10.8
20	RCT	Higher	50	76	0	39.6	30.4	24	Dairy products and meat (beef, pork, poultry, lamb, fish and offal)	25%	Ad libitum	Isotope Clearance (single intravenous injection of 51Cr-EDTA (3.7 MBq))	105.5	14.5	111.2	17.5
		Lower			0			24	Dairy products and meat (beef, pork, poultry, lamb, fish and offal)	12%	Ad libitum	Isotope Clearance (single intravenous injection of 51Cr-EDTA (3.7 MBq))	114.3	19	104.9	15.5
21	Cross	Higher	12	67	0	30.8	25.1	1	Meat, dairy products, and egg white powder	2g/kg	Isocaloric	MDRD	-	-	94.99	10.9
		Lower			0			1	Meat, dairy products, and egg white powder	0.5g/kg	Isocaloric	MDRD	-	-	91.97	9.85
22	Cross	Higher	10	70	0	60.2	25.8	1	Meat, dairy	2g/kg	Isocaloric	MDRD	-	-	76.64	9.26

#[a]	Design[b]	Group	Sample			Age[c]	BMI[d]	Time[e]	Protein Sources	Protein Intake[f]	Energy Intake[g]	GFR/eGFR Method[h]	GFR Pre[i]		GFR Post[i]	
			Total (N)	% Female	Diabetic (N)								Mean	SD	Mean	SD
									products, and egg white powder							
		Lower			0			1	Meat, dairy products, and egg white powder	0.5g/kg	Isocaloric	MDRD	-	-	69.2	9.55
23	Cross	Higher	10	50	0	24.3	23.3	1.5	-	2.08g/kg, 21.8%	2626	Iothalamate Clearance	-	-	127.8	5.7
		Lower			0			1.5	-	1.04g/kg, 11.1%	2615	Iothalamate Clearance	-	-	105.9	3.6
24	Cross	Higher	9	44	0	70	27.2	1.5	-	2.08g/kg, 21.8%	2296	Iothalamate Clearance	-	-	74	6.3
		Lower			0			1.5	-	1.04g/kg, 11.1%	2314	Iothalamate Clearance	-	-	81.3	6.5
25	RCT	Higher	64	0	0	50.8	33	52	3 serves low fat dairy, 300g lean red meat 4 times weekly, 100g deli-sliced meat or canned fish	35%, 142g/day	1675	Creatinine Clearance	106.4	24.9	109.7	39.5
		Lower			0			52	1 serves low fat dairy, 100g lean red meat 4 times weekly, 30g deli-sliced meat or canned fish	17%, 88g/day	1675	Creatinine Clearance	103.1	23.1	100.6	27.2

'-' indicates that data was not measured or reported.

a. Numbers refer to the following studies: 1 = (Bergstrom et al., 1985), 2 = (Brinkworth et al., 2004), 3 = (Brinkworth et al., 2010), 4 = (Chu et al., 1975), 5 = (Frank et al., 2009), 6 = (Friedman et al., 2012), 7 = (Hegsted et al., 1981), 8 = (Jenkins et al., 2001), 9 = (Johnston et al., 2004), 10 = (Juraschek et al., 2013), 11 = (Kerstetter et al., 1998), 12 = (Kim et al., 1979), 13 = (Larsen et al., 2011), 14 = (Leidy et al., 2007), 15 = (Luger et al., 2013), 16 = (Luscombe-Marsh et al., 2005), 17 = (Noakes et al., 2005), 18 = (Pomerleau et al., 1993), 19 = (Roughead et al., 2003), 20 = (Skov et al., 1999), 21 = (Wagner et al., 2007), 22 = (Wagner et al., 2007), 23 = (Walrand et al., 2008), 24 = (Walrand et al., 2008), 25 = (Wycherley et al., 2012)

b. Cross, crossover trial; RCT, randomized controlled trial.

c. Mean age measured in years.

d. Mean BMI, Body-Mass-Index, measured in kg/m^2.

e. Time of intervention measured in weeks.

f. Protein intake measured in g/kg body weight/day, % of energy intake/day, or total grams/day.

g. Energy intake measured in kcal/day.

[h.] GFR, glomerular filtration rate; MDRD, Modified Diet in Renal Disease calculation; CKD-Epi, Chronic Kidney Epidemiology Collaboration
[i.j.] GFR measured in mL/min.

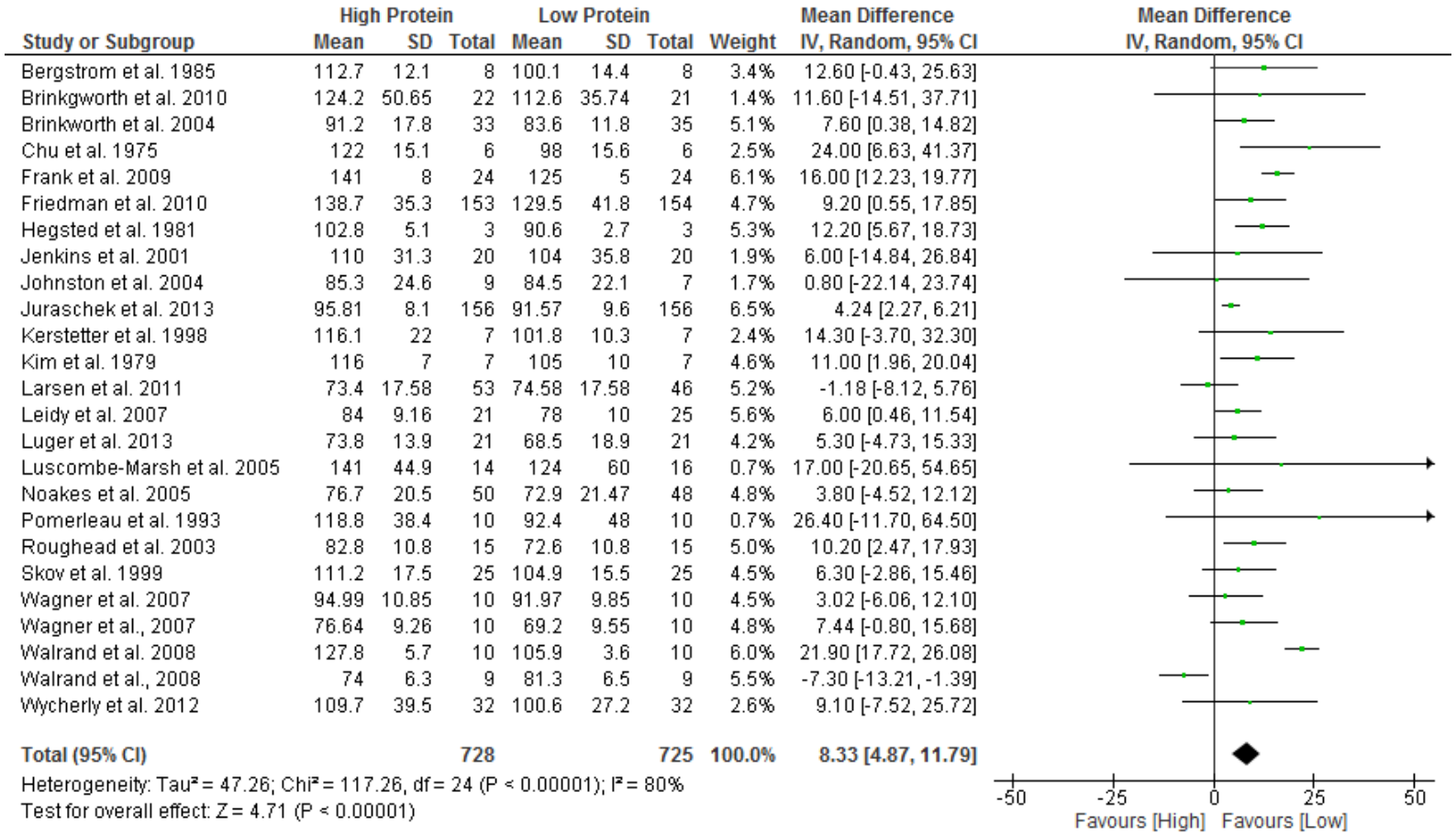


Figure 1. Forest plot showing pooled mean difference with 95% CI for post glomerular filtration rate (mL/min) of 25 randomized controlled high protein intake trials. Every trial's point estimate is represented by a shaded square along with a horizontal line outlining the upper and lower limits of the 95% CI. The area of the shaded square represents the relative weight of the study in this meta-analysis, corresponding to the percentage of weight listed. The shaded diamond represents the pooled mean differences of all of the trials with the 95% CI.

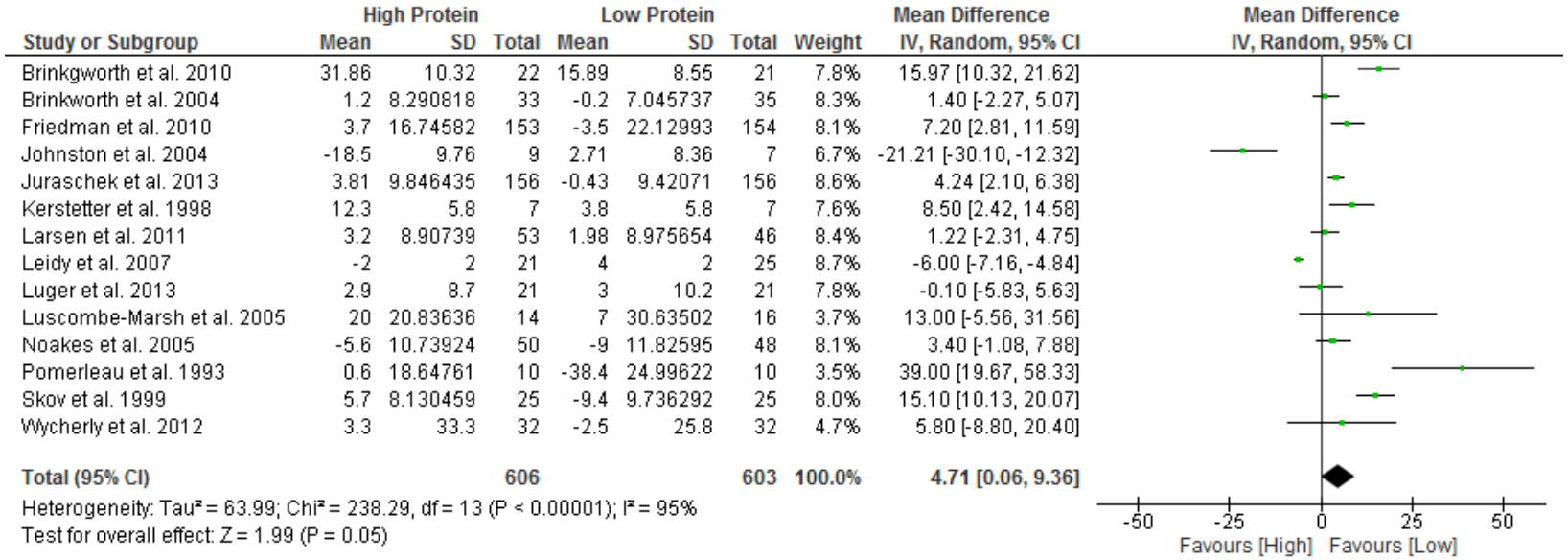


Figure 2. Forest plot showing pooled mean difference with 95% CI for change from baseline glomerular filtration rate (mL/min) of 14 randomized controlled high protein intake trials. Every trial's point estimate is represented by a shaded square along with a horizontal line outlining the upper and lower limits of the 95% CI. The area of the shaded square represents the relative weight of the study in this meta-analysis, corresponding to the percentage of weight listed. The shaded diamond represents the pooled mean differences of all of the trials with the 95% CI.

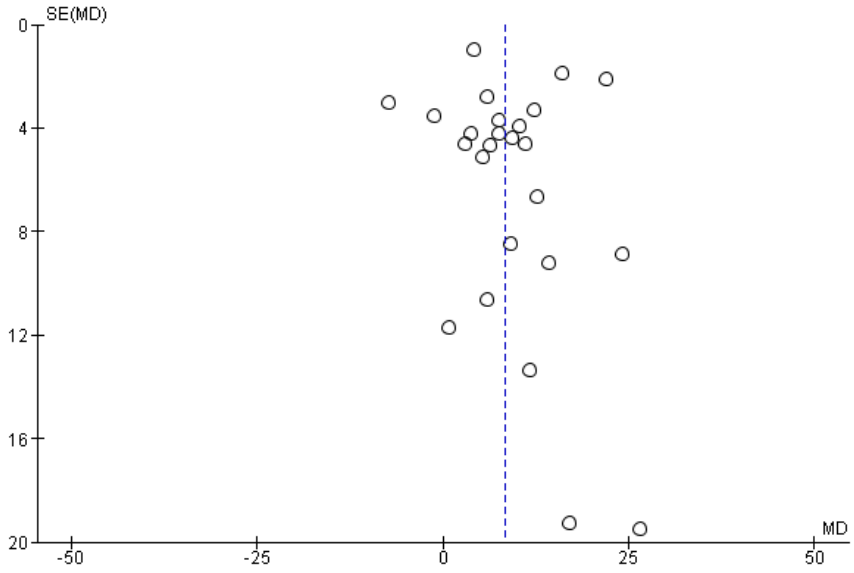


Figure 3. Funnel plot showing mean differences of post glomerular filtration rate (mL/min) of 25 randomized controlled trials for visual assessment of publication bias. Each circle represents the point estimate of a trial with the X-axis measuring mean difference and the Y-axis measuring the standard error of mean difference.

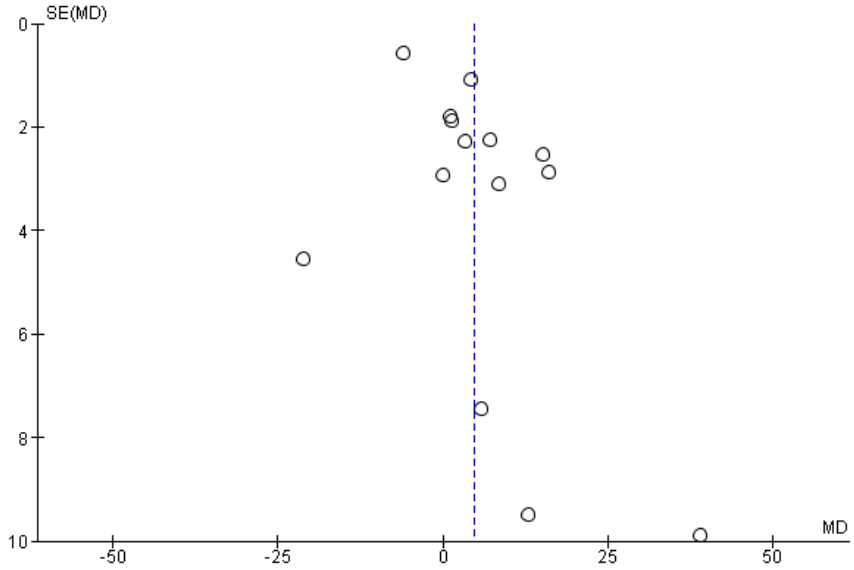


Figure 4. Funnel plot showing mean differences of change from baseline glomerular filtration rate (mL/min) of 14 randomized controlled trials for visual assessment of publication bias. Each circle represents the point estimate of a trial with the X-axis measuring mean difference and the Y-axis measuring the standard error of mean difference.

DISCUSSION

In the past few decades the traditional focus of research regarding the effect of dietary protein intake on renal health has shifted from studying populations with renal impairment to studying individuals of all demographics. This systematic review and meta-analyses is one of a few relatively recent reviews that have evaluated the effect of increased dietary protein intake on renal function in healthy populations. The purpose of this systematic review and meta-analysis was to determine the effect of high protein intake on GFR in populations living without any renal impairment. GFR was the main outcome of interest as it is widely accepted as the best measure of kidney function (Stevens & Levey, 2005). The main findings of this meta-analysis propose that increased dietary protein intake may increase GFR, however, given the heterogeneity presented and overestimation of intervention effects when using random- over fixed-effects meta-analysis, these interpretations can only be made with caution. Furthermore, although the mean difference in both analyses was significant, the mean difference when assessing change from baseline GFR versus post GFR was almost 50% less. Additionally, change from baseline GFR mean difference presented less funnel plot asymmetry despite having fewer studies, thus providing less indication of publication bias (Sterne et al., 2011). The reasoning for conducting an analysis looking solely at the change from baseline mean differences within each group was to allow for a more accurate depiction of intervention effects. The crossover trials utilized the same population for all interventions given the nature of the study. However, the remaining RCTs randomly divided the total subject population into two groups (or three in some cases) to receive separate treatments. Thus,

there was the possibility for one group to start with different demographics and most importantly a different baseline GFR. If the high protein intake group started with a higher baseline GFR for example, only evaluating the post GFR mean difference may not provide an accurate representation of the diet effects. This may have been the case with the study by Johnston et al. (2004), as the baseline GFR in mL/min for the high protein group was 103.8 while the corresponding starting value for the low protein group was 82. The ability to assess the data from two different perspectives for the same outcome provided the opportunity to compare these results to determine if there was a difference in the intervention effects; there was, but this may also be accounted for by the studies that were removed as a result of not having baseline measures.

Over the past decade, there have been several systematic reviews that have evaluated the effect of high protein intake on human physiology, however, few have assessed the effects of increased protein intake on kidney function in healthy populations. A recent systematic review of the effects of protein intake in heathy adults was performed by Pedersen, Kondrup and Borsheim (2013), but this study was limited solely to Nordic populations and only focused shortly on renal function. As a result of its inclusion criteria, only 4 studies were evaluated regarding the influence of increased protein consumption on kidney function (2 of which were RCTs and met the inclusion criteria for this review). Another review was published by Eisenstein, Roberts, Dallal, and Saltzman (2002). This review found that the literature current at that time was inconclusive with regards to high protein intake and renal function in healthy adults without renal disease. It found that a number of studies showed an increase in GFR alongside increased protein

intake (up to a saturation point of 125g/day), however, net hyperfiltration did not occur when renal mass was accounted for and protein intake was within 70 to 108 g/day (as higher protein intakes were linked to increased kidney mass). Furthermore, the review went on to describe the conflicting study results regarding health problems such as microalbuminuria and concluded by confirming the uncertainty of evidence illustrating negative impact (Eisenstein et al., 2002). This review was followed up in 2004 by Halton and Hu, which had very similar conclusions regarding insufficient evidence that high protein diets present a significant risk to renal function in healthy populations (Halton & Hu, 2004). The present systematic review and meta-analysis found similar results to Eisenstein et al. (2002) and Halton and Hu (2004) as it is uncertain whether high dietary protein intake conclusively influences an increase in GFR.

The most recent and comparable review to the present meta-analysis was published in 2014 by Schwingshackl & Hoffman. This review also evaluated the effects of high versus low protein diets on renal function in subjects without chronic kidney disease. This article assessed a number of kidney measures but its main outcome parameter was GFR. Schwingshackl & Hoffman (2014) concluded by stating that high protein diets were associated with increased GFR and recommending HP diets should be followed with caution. The latter statement is correct as studies have illustrated conflicting evidence regarding high dietary protein intake on renal function and there is insufficient data to confirm a negative response. However, concerns were raised with the process in arriving at this conclusion. The meta-analysis conducted by Schwingshackl & Hoffman (2014) only calculated mean differences in post GFR values. Problems that may

arise with these methods have been explained above and not evaluating the change from baseline GFR values may have resulted in overestimated intervention effects.

One more important concept to consider is the interpretation of a rise in GFR with increased dietary protein intake. Decades ago, Brenner, Meyer, and Hostetter (1982) suggested that increases in GFR might lead to renal dysfunction and increase the risk of experiencing a renal injury. This has been followed up over the years with evidence that lower protein diets can slow the progression of disease in individuals living with CKD, as well as corollary logic associating increased GFR caused by high dietary protein intake with potential renal dysfunction (Frank et al., 2009; Klahr et al., 1994; Schwingshackl & Hoffmann, 2014). However, a review of the literature by Martin, Armstrong, and Rodriguez (2005) also states that the research lacks a clear link between high protein intake and the initiation of chronic kidney disease in healthy populations. It also points towards the potential for the increase in GFR to be a physiological adaptation to high protein intake that is a function of a renal reserve. This is a hypothesis backed by a number of other authors (Bosch et al., 1983; Fliser, Zeier, Nowack, & Ritz, 1993). A very recent editorial by Bie & Astrup (2015) summarizes a few of the studies involving high protein interventions and renal function; the changes seen in GFR are accompanied by corresponding increases/decreases in renal size and appear to be reversible. Thus, the association of high protein intake with increased GFR in the present analysis may also have been the result of physiological adaptations in the subjects within safe kidney functioning levels.

Limitations

Due to the inclusion and exclusion criteria of this systematic review some limitations when interpreting results are raised. The existing literature studying high protein intake and renal function in healthy populations is limited; the inclusion criteria had to be quite broad in its scope to acquire as many relevant articles as possible. As can be seen in Table 1, the diets varied significantly between trials. While a certain threshold had to be met regarding the level of protein intake in the high protein group to be included in the present analysis, the level of absolute and relative protein intake still varied greatly between studies. These differences occur to a greater extent when considering the differences in total energy intake as well. Moreover, the intervention periods ranged from one week to over a year; this may have influenced greater physiological adaptation by individual organ systems and may have contributed to the different experiences in diet adherence. The latter was addressed differently between the trials, but typically concerns with recall bias were consistently expressed. While the purpose of this review was aimed at addressing healthy populations living without pre-existing renal impairments, the demographics of the population varied extensively. As such, this contributed to the high heterogeneity that was reported and concerns with complete generalizability to the broader public.

Another limitation to this review was the range of GFR measures and calculations used. As a result of incorporating trials as far back as 1975 and the inability to restrict inclusion based on methods used (due to limited research), the GFR measures included

creatinine clearance, modifications of creatinine clearance that adjust for demographics, and various inulin/isotope clearances. Research illustrates the potential for creatinine clearance measures to underestimate GFR, as well as the increased accuracy presented by iGFR and eGFR measures (Levey et al., 1999; Michels et al., 2010).

A limitation of this study but also a strength was the efforts made to look at change from baseline mean differences. While this is not a novel approach to assessing intervention effects in meta-analyses, it is the first of its kind regarding high protein intake on renal function in healthy populations. However, not all baseline values were obtainable which resulted in a number of studies being excluded from this analysis. Furthermore, SDΔ was not always reported and this had to be averaged and estimated using calculations from the Cochrane Handbook for Systematic Review of Interventions (The Cochrane Collaboration, 2011). While this is an accepted method by Cochrane, it is not as accurate as it could be if SDΔ were calculated and reported in all trials by the original authors and researchers.

Despite its limitations, the present systematic review and meta-analysis provides an excellent checkpoint for further research as a result of its thorough search strategy and evaluation of high protein influence on GFR from two different perspectives. Future studies should continue to evaluate the effect of high protein intake on renal function as it is a field of research that still lacks a plethora of evidence. Additionally, when conducting such research it is crucial to include baseline measures in publication, change from baseline mean differences and SDΔ as this allows for better evaluations of intervention

effects. Regarding GFR, efforts should also be made to use the most accurate up to date measures; using creatinine clearance without demographic-adjusting calculations does not produce the best validity or reliability (Levey et al., 1999). Lastly, future studies as well as reviews should first and foremost ensure accurate measures of GFR as it is widely accepted as the best measure of renal function, and should also evaluate other health indicators such as kidney mass as there is evidence that this correlates with changes in GFR and may in fact be reversible (confirming the notion of physiological adaptation).

Conclusion

High protein diets may be associated with increases in GFR but the results of this meta-analysis suggest this to be inconclusive. Additionally, there is uncertainty whether increased GFR may actually lead to renal impairment as research illustrates the possibility of this being a physiological adaptation within a healthy capacity for the kidney. To date, there is little evidence that suggests negative impact on renal function with increased dietary protein intake. Therefore, while caution should still be used when determining whether increasing protein intake is appropriate for an individual, particularly in populations with pre-existing health conditions or renal impairment, the current research and literature suggests that undertaking such a diet may not lead to any concerns regarding the kidneys.

In the context of population health among both developed and developing countries, the findings presented throughout this systematic review and meta-analyses have varied implications. As noted in the results, the current evidence is insufficient to

state that higher protein intake conclusively increases GFR and that this leads to progressive renal disease. The absence of this does not mean that an increase in dietary protein intake is recommended for all communities around the world, however, this should be taken into consideration when responding to the impacts of the ever-increasing global consumption of protein. Moreover, these results have different consequences internationally when evaluating the current obesity pandemic. Specifically, important factors to consider when interpreting the results of this review are: the heterogeneity of the global population, the sustainability of protein consumption, and rising middle-class populations who are consuming more protein (in particular from meat sources) around the world.

An important factor that led to the inconclusive results of the present analysis was the heterogeneity of the included trials. Heterogeneity influences the interpretation of these results when evaluating the global population as well. When assessing factors affecting weight gain, obesity, and renal function, there are a number of influences that may have a role in the response to an intervention. Factors such as age, current BMI, and sex are just a few demographic measures that may influence adherence or response to a change in diet. Additionally, factors including genetic predisposition, which may be clustered by different racial sub-groupings, and physiological adaptation also greatly affect the result of an intervention in an individual. Therefore, it is apparent that there is no ‘one size fits all’ solution regarding potential solutions to combat obesity (i.e. higher protein diets) and the corresponding impact on the human body (i.e. renal function). International population heterogeneity will continue to exist and due diligence should be

exercised by academics to look for potential solutions with sustainable future direction. A rise in popularity of higher protein diets may be a potential long-term solution to aid in the fight against obesity in many communities, but the current global increase in meat consumption is evidently not an environmentally sustainable solution (Tilman, Cassman, Matson, Naylor, & Polasky, 2002).

There has been a focus on the potential for higher protein diets to provide a beneficial weight loss strategy that preserves or increases lean mass – a potential solution to obesity at the individual and population level. However, the source from which an increase in protein intake occurs is another important factor to consider. If communities increase meat consumption in an effort to preserve muscle mass for example, there may be further consequences in terms of personal health and the environment. Regarding personal health, care should be taken to ensure an increase in meat consumption is not accompanied by an increase in saturated fat or sodium intake if this exceeds the healthy upper limits for an individual (Lichtenstein et al., 2006). Additionally, another important factor to consider is whether this increase in meat consumption is a sustainable solution, both locally and globally (Tilman et al., 2002). It is apparent that the current rate of livestock consumption internationally is not sustainable (Herrero, Thornton, Gerber, & Reid, 2009). Thus, while high protein diets remain a potential avenue through which individuals may pursue weight loss, to be effective at an international level the major sources of dietary protein may have to be plant-based. Interestingly, a highly plant-based but higher protein diet is an approach that has been shown clinically to be very effective in aiding weight loss and improving blood lipids (Jenkins et al., 2009, 2014). Although

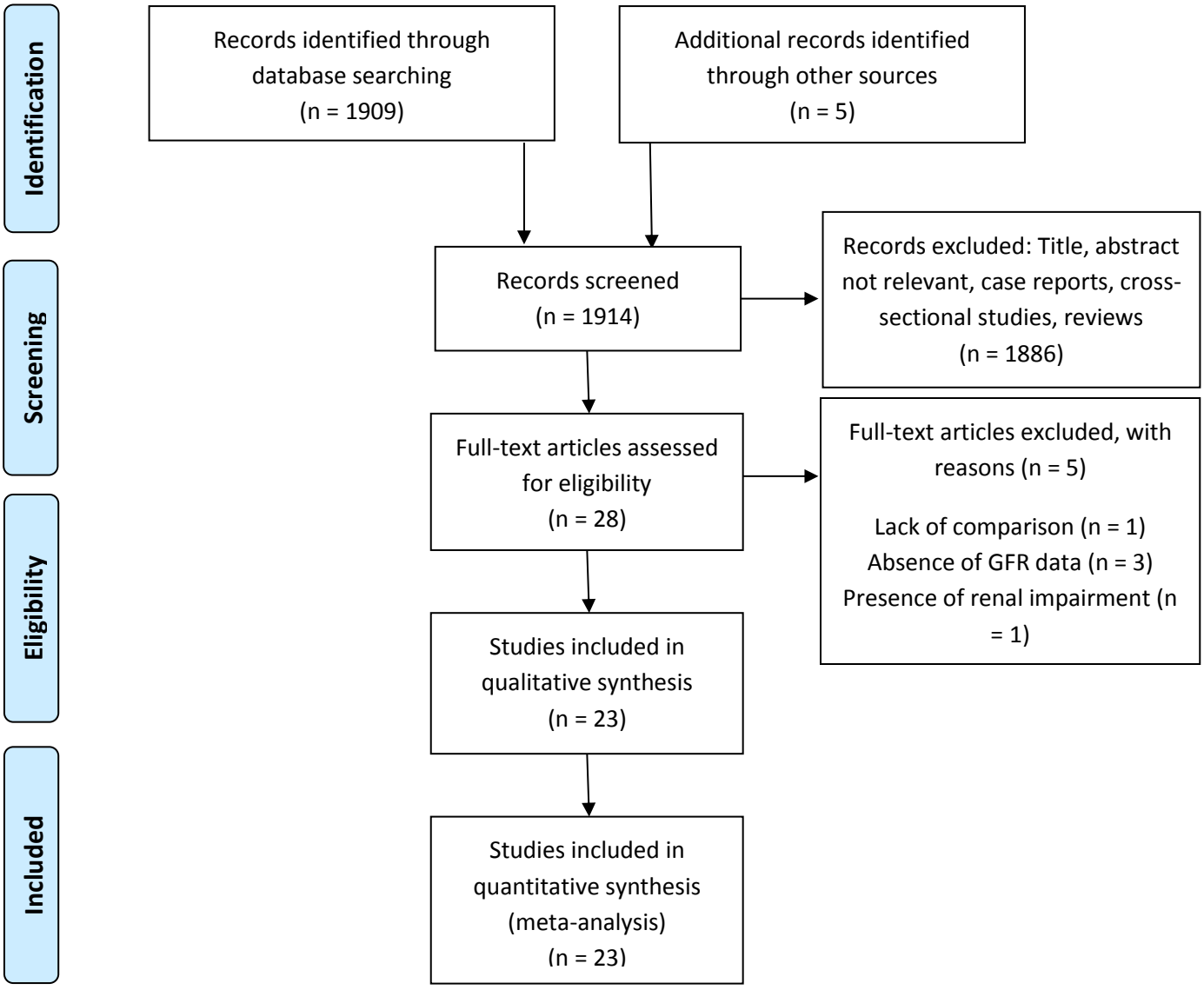
protein quality is generally lower in plants versus meats, all essential amino acids can be adequately obtained from plant sources (Food and Agriculture Organization of the United Nations, 2013; Jackson, 1983). Therefore, the absence of a negative impact on renal function with higher protein diets may provide further incentive to undertake such a diet, but sustainability of the diet at the individual and population level should be considered.

Lastly, the current obesity pandemic has been illustrated thoroughly and there is evidence that increased allocation of income towards meat is occurring in the growing middle-class globally (Senauer & Goetz, 2003). Insofar as kidney function and glomerular filtration rate are concerned the absolute increase in protein consumption does not, based on the present analysis, appear to be harmful. However, accompanying this rise in family income is a rise not only in protein/meat intake, but also in total energy intake (Delgado, 2003; Senauer & Goetz, 2003). As outlined previously, the double burden of disease that exists in developing countries continues to be a problem and the comorbidities of overweight and obesity is a rising issue. The results of this analysis suggest that national health concerns should continue to address obesity and potentially look to advocate for higher protein diets, from mixed protein sources, to combat weight gain in healthy renal populations. Sustainable (plant-based) sources of protein should be emphasized as well as healthy sources of protein that are lower in energy (i.e., not accompanied by fat) and sodium content. It is evident that obesity is rising globally, in both developing and developed countries, thus drastic changes are necessary. However, regardless of decisions to back higher protein diets as a weight loss strategy, current evidence illustrates that healthy individuals who embark on such a diet would not

experience a negative impact on renal function. With the current levels of overweight and obesity worldwide, research moving forward should be conducted on higher protein energy-restricted diets and renal function to evaluate whether long-term adherence results in positive results regarding lean mass preservation and renal function. The sources of dietary protein should be from mixed sources and could perhaps be primarily plant-based. Efforts should be made to run these trials in as large and diverse sample sizes as possible. These factors would take into account the concerns raised in this discussion and will as a result reduce potential limitations when generalizing results to the broader global public. The potential metabolic effects of higher protein diets is backed by evidence-based systematic reviews and meta-analyses, but continued research on the potential influences on overall human physiology is necessary to comprehensively determine the viability of said diets as a way of combatting the current obesity pandemic.

APPENDIX

Appendix 1. Flowchart of study inclusion screening process.



Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. Doi:10.1371/journal.pmed1000097

Appendix 2. Table listing change from baseline glomerular filtration rate means and change standard deviation for 14 randomized controlled trials included in the meta-analysis in Figure 2.

Study name	HP Mean Diff	SD change	n	LP Mean Diff	SD change	n
Brinkworth et al., 2004	31.86	10.32	22	15.89	8.55	21
Brinkworth et al., 2010	1.2	8.290818	33	-0.2	7.045737	35
Friedman et al., 2012	3.7	16.74582	153	-3.5	22.12993	154
Johnston et al., 2004	-18.5	9.76	9	2.71	8.36	7
Juraschek et al., 2013	3.81	9.846435	156	-0.43	9.42071	156
Kerstetter et al., 1998	12.3	5.8	7	3.8	5.8	7
Larsen et al., 2011	3.2	8.90739	53	1.98	8.975654	46
Leidy et al., 2007	-2	2	21	4	2	25
Luger et al., 2013	2.9	8.7	21	3	10.2	21
Luscombe-Marsh et al., 2005	20	20.83636	14	7	30.63502	16
Noakes et al., 2005	-5.6	10.73924	50	-9	11.82595	48
Pomerleau et al., 1993	0.6	18.64761	10	-38.4	24.99622	10
Skov et al., 1999	5.7	8.130459	25	-9.4	9.736292	25
Wycherley et al., 2012	3.3	33.3	32	-2.5	25.8	32

Appendix 3. EMBASE Search Strategy

Database: Embase <1974 to 2015 June 03>

Search Strategy:

---

1 exp Dietary Proteins/ (32506)

2 amino acids/ or exp amino acids, essential/ (378746)

3 exp Diet, Protein-Restricted/ or exp Diet, Vegetarian/ (8423)

4 exp fish protein/ (1819)

5 exp vegetable protein/ (116979)

6 ((egg* or yolk* or milk or animal* or diet*) adj3 protein*).tw. (42064)

7 (amino adj2 acid* adj4 (essential* or nonessential* or non essential* or dispensable* or nondispensable* or non dispensable*)).tw. (9069)

8 ((Soy or soy bean* or soybean* or plant or vegetable* or fish) adj3 protein*).tw. (14912)

9 ((vegan* or vegetarian*) and protein*).tw. (743)

10 ((diet* or balance*) adj3 nitrogen*).tw. (6133)

11 protein metabolism/ (21106)

12 nitrogen metabolism/ (2469)

13 (diet* adj3 (low protein* or protein restrict* or protein free or high protein or protein control*)).tw. (8597)

14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (577788)

15 (intake* or timing* or frequen* or requirement* or utili?ation* or metabolism*).tw. (2760421)

16 nutritional requirement/ (16006)

17 15 or 16 (2768384)

18 14 and 17 (100911)

19 exp glomerulus filtration rate/ (58259)

20 exp inulin clearance/ or exp inulin/ (8410)

21 exp kidney circulation/ (2751)

22 ((kidney* or renal*) adj2 function*).tw. (115792)

23 (renal adj3 (flow* or circulat*)).tw. (17039)

24 (((kidney* or renal*) adj2 (calculi or calculus or stone*)) or nephrolithiasis).tw. (18007)

25 glomerul$.mp. (171015)

26 exp proteinuria/ (72308)

27 exp albuminuria/ (21822)

28 exp creatinine/ (111621)

29 glomerular filtration rate.ti,ab. (37512)

30 inulin.ti,ab. (7808)

31 proteinuria.ti,ab. (40620)

32 albuminuria.ti,ab. (9588)

33 hemoglobinuria.ti,ab. (3572)

34 creatinine.ti,ab. (120325)

35 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or

32 or 33 or 34 (431994)

36 18 and 35 (3920)

37 36 not (mice* or mouse* or rat or rats).tw. (3179)

38 remove duplicates from 37 (3150)

39 limit 38 to english language (2803)

40 random:.tw. or clinical trial:.mp. or exp health care quality/ (3541269)

41 39 and 40 (668)

****

Appendix 4. MEDLINE Search Strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

---

1 exp Proteinuria/ (33687)

2 proteinuria.ti,ab. (30597)

3 albuminuria.ti,ab. (7443)

4 hemoglobinuria.ti,ab. (2831)

5 or/2-4 (39559)

6 1 or 5 (56642)

7 Creatinine/ (48355)

8 creatinine.ti,ab. (83477)

9 7 or 8 (104204)

10 Glomerular Filtration Rate/ (34391)

11 glomerular filtration rate.ti,ab. (28938)

12 Inulin/ (6160)

13 inulin.ti,ab. (6917)

14 exp Renal Circulation/ (12100)

15 ((kidney or renal) adj2 function*).tw. (83047)

16 ((kidney* or renal*) adj2 function*).tw. (83559)

17 (renal* adj3 (flow* or circulat*)).tw. (14829)

18 (((kidney* or renal*) adj2 (calculi or calculus or stone*)) or nephrolithiasis).tw. (12795)

19 glomerul*.mp. (134309)

20 1 or 2 or 3 or 4 or 7 or 8 or 10 or 11 or 12 or 13 or 14 or 16 or 17 or 18 or 19 (309568)

21 1 or 7 or 10 or 12 or 14 or 16 or 17 or 18 or 19 (263560)

22 20 not 21 (46008)

23 (intake* or timing or frequen* or requirement* or utili?ation* or metabolism*).tw. (2211370)

24 nutritional requirements/ (17319)

25 23 or 24 (2219847)

26 exp dietary proteins/ (81203)

27 amino acids/ or exp amino acids, essential/ (289129)

28 diet, protein-restricted/ or diet, vegetarian/ or diet, macrobiotic/ (4697)

29 exp Fish Proteins/ (11669)

30 exp Plant Proteins/ (145645)

31 ((egg* or yolk* or milk or animal* or diet*) adj3 protein*).tw. (36582)

32 (amino adj2 acid* adj4 (essential* or nonessential* or non essential* or dispensable* or nondispensable* or non dispensable*)).tw. (7759)

33 ((soy or soy bean* or soybean* or plant or vegetable* or fish) adj3 protein*).tw. (13720)

34 ((vegan* or vegetarian*) and protein*).tw. (577)

35 ((diet* or balance*) adj3 nitrogen*).tw. (5471)

36 proteins/ and me.fs. (98217)

37 nitrogen/ and me.fs. (30246)

38 (diet* adj3 (low protein* or protein restrict* or protein free or high protein or protein control*)).tw. (7302)

39 or/26-38 (642640)

40 21 and 25 and 39 (2623)

41 20 and 25 and 39 (3224)

42 41 not (mice* or mouse* or rat or rats).tw. (2552)

43 remove duplicates from 42 (2495)

44 limit 43 to english language (2217)

45 clinical trial.mp. or clinical trial.pt. or random*.mp. or tu.xs. (4334242)

46 44 and 45 (1241)

REFERENCES

Al-Rodhan, N. R., & Stoudmann, G. (2006). Definitions of globalization: A comprehensive overview and a proposed definition. *Geneva Centre for Security Policy*.

Arbex, A. K., Rocha, D. R., Aizenberg, M., & Ciruzzi, M. S. (2014). Obesity epidemic in Brazil and Argentina: a public health concern. *Journal of health, population, and nutrition*, *32*(2), 327.

Barnard, N. D. (2010). Trends in food availability, 1909–2007. *The American journal of clinical nutrition*, *91*(5), 1530-1536.

Bauer, J., Biolo, G., Cederholm, T., Cesari, M., Cruz-Jentoft, A. J., Morley, J. E., … Boirie, Y. (2013). Evidence-based recommendations for optimal dietary protein intake in older people: A position paper from the prot-age study group. *Journal of the American Medical Directors Association*, *14*(8), 542–559. http://doi.org/10.1016/j.jamda.2013.05.021

Baumgartner, R. N., Wayne, S. J., Waters, D. L., Janssen, I., Gallagher, D., & Morley, J. E. (2004). Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obesity Research*, *12*(12), 1995–2004. http://doi.org/10.1038/oby.2004.250

Bergström, J., Ahlberg, M., & Alvestrand, a. (1985). Influence of protein intake on renal hemodynamics and plasma hormone concentrations in normal subjects. *Acta Medica Scandinavica*, *217*(2), 189–196.

Bie, P., & Astrup, A. (2015). *Dietary protein and kidney function: when glomerular filtration rate is desirable*. Retrieved from file:///C:/Users/Arjun/Downloads/ajcn.115.112672.full (2).pdf

Borst, S. E. (2004). Interventions for sarcopenia and muscle weakness in older people. *Age and Ageing*. http://doi.org/10.1093/ageing/afh201

Bosch, J. P., Saccaggi, A., Lauer, A., Ronco, C., Belledonne, M., & Glabman, S. (1983). Renal functional reserve in humans. Effect of protein intake on glomerular filtration rate. *The American Journal of Medicine*, *75*(6), 943–950. http://doi.org/10.1016/0002-9343(83)90873-2

Brenner, B. M., Meyer, T. W., & Hostetter, T. H. (1982). Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging,

renal ablation, and intrinsic renal disease. *The New England Journal of Medicine*, *307*(11), 652–9. http://doi.org/10.1056/NEJM198209093071104

Brinkworth, G. D., Buckley, J. D., Noakes, M., & Clifton, P. M. (2010). Renal Function Following Long-Term Weight Loss in Individuals with Abdominal Obesity on a Very-Low-Carbohydrate Diet vs High-Carbohydrate Diet. *Journal of the American Dietetic Association*, *110*(4), 633–638. http://doi.org/10.1016/j.jada.2009.12.016

Brinkworth, G. D., Noakes, M., Keogh, J. B., Luscombe, N. D., Wittert, G. a, & Clifton, P. M. (2004). Long-term effects of a high-protein, low-carbohydrate diet on weight control and cardiovascular risk markers in obese hyperinsulinemic subjects. *International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity*, *28*(5), 661–670. http://doi.org/10.1038/sj.ijo.0802766

Bruinsma, J. (2003). *World agriculture : towards 2015 / 2030*. *Earthscan Publications Ltd London*.

CDC. (2012). Defining adult overweight and obesity. Retrieved July 2, 2015, from http://www.cdc.gov/obesity/adult/defining.html

Chen, Y., Copeland, W. K., Vedanthan, R., Grant, E., Lee, J. E., Gu, D., … Potter, J. D. (2013). Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium. *BMJ (Clinical Research Ed.)*, *347*, f5446. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3788174&tool=pmcentrez&rendertype=abstract

Chu, J. Y., Margen, S., & Costa, F. M. (1975). Studies in calcium metabolism. II. Effects of low calcium and variable protein intake on human calcium metabolism. *The American Journal of Clinical Nutrition*, *28*(9), 1028–1035.

Delanaye, P., Schaeffner, E., Ebert, N., Cavalier, E., Mariat, C., Krzesinski, J.-M., & Moranne, O. (2012). Normal reference values for glomerular filtration rate: what do we really know? *Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association*, *27*(7), 2664–72. http://doi.org/10.1093/ndt/gfs265

Delgado, C. L. (2003). Rising consumption of meat and milk in developing countries has created a new food revolution. *The Journal of Nutrition*, *133*(11 Suppl 2), 3907S–3910S. http://doi.org/0022-3166/03

Eisenstein, J., Roberts, S. B., Dallal, G., & Saltzman, E. (2002). High-protein weight-loss diets: are they safe and do they work? A review of the experimental and

epidemiologic data. *Nutrition Reviews*, *60*(7 Pt 1), 189–200. http://doi.org/10.1301/00296640260184264

Fiddes, N. (2004). *Meat: A Natural Symbol*. Routledge. Retrieved from https://books.google.com/books?hl=en&lr=&id=jSqIAgAAQBAJ&pgis=1

Flegal, K. M., Kit, B. K., Orpana, H., & Graubard, B. I. (2013). Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA : The Journal of the American Medical Association*, *309*(1), 71–82. http://doi.org/10.1001/jama.2012.113905

Fliser, D., Zeier, M., Nowack, R., & Ritz, E. (1993). Renal functional reserve in healthy elderly subjects. *Journal of the American Society of Nephrology : JASN*, *3*(7), 1371–1377.

Food and Agriculture Organization of the United Nations. (2013). Dietary protein quality evaluation in human nutrition. Retrieved July 2, 2015, from http://www.fao.org/ag/humannutrition/35978-02317b979a686a57aa4593304ffc17f06.pdf

Fouque, D., & Aparicio, M. (2007). Eleven reasons to control the protein intake of patients with chronic kidney disease. *Nature Clinical Practice. Nephrology*, *3*(7), 383–392. http://doi.org/10.1038/ncpneph0524

Fouque, D., & Laville, M. (2009). Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database of Systematic Reviews*. http://doi.org/10.1002/14651858.CD001892.pub3

Frank, H., Graf, J., Amann-Gassner, U., Bratke, R., Daniel, H., Heemann, U., & Hauner, H. (2009). Effect of short-term high-protein compared with normal-protein diets on renal hemodynamics and associated variables in healthy young men. *American Journal of Clinical Nutrition*, *90*(6), 1509–1516. http://doi.org/10.3945/ajcn.2009.27601

Frestedt, J. L., Zenk, J. L., Kuskowski, M. A., Ward, L. S., & Bastian, E. D. (2008). A whey-protein supplement increases fat loss and spares lean muscle in obese subjects: a randomized human clinical study. *Nutrition & Metabolism*, *5*, 8. http://doi.org/10.1186/1743-7075-5-8

Friedman, A. N. (2004). High-protein diets: Potential effects on the kidney in renal health and disease. *American Journal of Kidney Diseases*. http://doi.org/10.1053/j.ajkd.2004.08.020

Friedman, A. N., Ogden, L. G., Foster, G. D., Klein, S., Stein, R., Miller, B., … Wyatt, H. R. (2012). Comparative effects of low-carbohydrate high-protein versus low-fat diets on the kidney. *Clinical Journal of the American Society of Nephrology*, *7*(7), 1103–1111. http://doi.org/10.2215/CJN.11741111

Gaffney-Stomberg, E., Insogna, K. L., Rodriguez, N. R., & Kerstetter, J. E. (2009). Increasing dietary protein requirements in elderly people for optimal muscle and bone health. *Journal of the American Geriatrics Society*. http://doi.org/10.1111/j.1532-5415.2009.02285.x

Gilpin, R., & Gilpin, J. (2000). The Second Great Age of Capitalism. In *The Challenge of Global Capitalism*. Retrieved from http://www.nytimes.com/books/first/g/gilpin-capitalism.html

Grigg, D. (1996). The Starchy Staples in World Food Consumption. *Annals of the Association of American Geographers*. http://doi.org/10.1111/j.1467-8306.1996.tb01760.x

Halton, T. L., & Hu, F. B. (2004). The effects of high protein diets on thermogenesis, satiety and weight loss: a critical review. *Journal of the American College of Nutrition*, *23*(5), 373–385. http://doi.org/10.1080/07315724.2004.10719381

Hegsted, M., & Linkswiler, H. M. (1981). Long-term effects of level of protein intake on calcium metabolism in young adult women. *The Journal of Nutrition*, *111*(2), 244–251.

Herrero, M., Thornton, P. K., Gerber, P., & Reid, R. S. (2009). Livestock, livelihoods and the environment: understanding the trade-offs. *Current Opinion in Environmental Sustainability*, *1*(2), 111–120. http://doi.org/10.1016/j.cosust.2009.10.003

Hoffman, B. (2014). How increased meat consumption in China changes landscapes across the globe. Retrieved July 2, 2015, from http://www.forbes.com/sites/bethhoffman/2014/03/26/how-increased-meat-consumption-in-china-changes-landscapes-across-the-globe/

Hoffman, J., & Falvo, M. (2004). Protein-Which is best. *Journal of Sports Science and Medicine*, *3*(2004), 118–130. Retrieved from http://jssm.org/vol3/n3/2/v3n3-2pdf.pdf\nhttp://www.jssm.org/vol3/n3/2/v3n3-2pdf.pdf?utm_source=REFERENCES_R7

Huff, M. W., & Carroll, K. K. (1980). Effects of dietary protein on turnover, oxidation, and absorption of cholesterol, and on steroid excretion in rabbits. *Journal of Lipid Research*, *21*(5), 546–548.

Jackson, A. (1983). Amino acids: essential and non-essential? *The Lancet*, *321*(8332), 1034–1037. http://doi.org/10.1016/S0140-6736(83)92656-9

Jafar, T. H., Stark, P. C., Schmid, C. H., Landa, M., Maschio, G., de Jong, P. E., … Levey, A. S. (2003). Progression of Chronic Kidney Disease : The Role of Blood Pressure COntrol, Proteinuria, and Angiotensin-Converting Enzyme Inhibition. *Ann Intern Med*, *139*(4), 244–252. http://doi.org/139/4/244 [pii]

Jenkins, D. J. a, Kendall, C. W. C., Vidgen, E., Augustin, L. S. a, Van Erk, M., Geelen, A., … Connelly, P. W. (2001). High-protein diets in hyperlipidemia: Effect of wheat gluten on serum lipids, uric acid, and renal function. *American Journal of Clinical Nutrition*, *74*(1), 57–63.

Jenkins, D. J. A., Wong, J. M. W., Kendall, C. W. C., Esfahani, A., Ng, V. W. Y., Leong, T. C. K., … Singer, W. (2009). The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Archives of Internal Medicine*, *169*(11), 1046–54. http://doi.org/10.1001/archinternmed.2009.115

Jenkins, D. J. A., Wong, J. M. W., Kendall, C. W. C., Esfahani, A., Ng, V. W. Y., Leong, T. C. K., … Singer, W. (2014). Effect of a 6-month vegan low-carbohydrate ('Eco-Atkins') diet on cardiovascular risk factors and body weight in hyperlipidaemic adults: a randomised controlled trial. *BMJ Open*, *4*(2), e003505–e003505. http://doi.org/10.1136/bmjopen-2013-003505

Johnston, C. S., Tjonn, S. L., & Swan, P. D. (2004). High-protein, low-fat diets are effective for weight loss and favorably alter biomarkers in healthy adults. *The Journal of Nutrition*, *134*(3), 586–591.

Joint WHO/FAO/UNU Expert Consultation. (2007). Protein and amino acid requirements in human nutrition. *World Health Organization Technical Report Series*, (935), 1–265, back cover. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18330140

Josse, A. R., Atkinson, S. A., Tarnopolsky, M. A., & Phillips, S. M. (2011). Consumption of higher dairy and dietary protein during diet- and exercise-induced weight loss promotes a metabolically favourable body composition change in overweight and obese young women. *FASEB Journal*, *25*. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed10&AN=70753457\nhttp://sfx.ubn.ru.nl/sfx_local?sid=OVID:embase&id=pmid:&id=doi:&issn=0892-6638&isbn=&volume=25&issue=&spage=&pages=&date=2011&title=FASEB+Journal&atitle=Consumption+o

Juraschek, S. P., Appel, L. J., Anderson, C. A. M., & Miller, E. R. (2013). Effect of a high-protein diet on kidney function in healthy adults: results from the OmniHeart trial. *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation*, *61*(4), 547–54. http://doi.org/10.1053/j.ajkd.2012.10.017

Kanter, R. M. (2003). Thriving Locally in the Global Economy. *Harvard Business Review*. http://doi.org/10.1016/S0024-6301(97)86604-6

Kasiske, B., Lakatua, J., Ma, J., & Louis, T. (1998). A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *American Journal of Kidney Diseases*, *31*(6), 954–961. http://doi.org/10.1053/ajkd.1998.v31.pm9631839

Kennedy, G., Nantel, G., & Shetty, P. (2004). Globalization of food systems in developing countries: impact on food security and nutrition. *FAO Food and Nutrition Paper*, *83*, 1–300. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19178111

Kerr, M., & Charles, N. (1986). Servers and Providers: The Distribution of Food within the Family. *Sociological Review*, *34*(1), 115–157.

Kerstetter, J. E., O'Brien, K. O., & Insogna, K. L. (1998). Dietary protein affects intestinal calcium absorption. *The American Journal of Clinical Nutrition*, *68*(4), 859–865.

Kim, Y., & Linkswiler, H. M. (1979). Effect of level of protein intake on calcium metabolism and on parathyroid and renal function in the adult human male. *The Journal of Nutrition*, *109*(8), 1399–1404.

Klahr, S., Levey, A. S., Beck, G. J., Caggiula, A. W., Hunsicker, L., Kusek, J. W., & Striker, G. (1994). The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*, *330*(13), 877–884. http://doi.org/10.1056/NEJM199403313301301

Krieger, J. W., Sitren, H. S., Daniels, M. J., & Langkamp-Henken, B. (2006). Effects of variation in protein and carbohydrate intake on body mass and composition during energy restriction: a meta-regression 1. *The American Journal of Clinical Nutrition*, *83*(2), 260–74. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16469983

Lambin, E. F., & Meyfroidt, P. (2011). Global land use change, economic globalization, and the looming land scarcity. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(9), 3465–3472. http://doi.org/10.1073/pnas.1100480108

Larsen, R. N., Mann, N. J., Maclean, E., & Shaw, J. E. (2011). The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: A 12 month randomised controlled trial. *Diabetologia*, *54*(4), 731–740. http://doi.org/10.1007/s00125-010-2027-y

Layman, D. K. (2004). Protein quantity and quality at levels above the RDA improves adult weight loss. *Journal of the American College of Nutrition*, *23*(6 Suppl), 631S–636S. http://doi.org/10.1080/07315724.2004.10719435

Layman, D. K., Anthony, T. G., Rasmussen, B. B., Adams, S. H., Lynch, C. J., Brinkworth, G. D., & Davis, T. A. (2015). Defining meal requirements for protein to optimize metabolic roles of amino acids. *American Journal of Clinical Nutrition*. http://doi.org/10.3945/ajcn.114.084053

Leidy, H. J., Carnell, N. S., Mattes, R. D., & Campbell, W. W. (2007). Higher protein intake preserves lean mass and satiety with weight loss in pre-obese and obese women. *Obesity (Silver Spring, Md.)*, *15*(2), 421–429. http://doi.org/10.1038/oby.2007.531

Leidy, H. J., Clifton, P. M., Astrup, A., Wycherley, T. P., Westerterp-Plantenga, M. S., Luscombe-Marsh, N. D., … Mattes, R. D. (2015). The role of protein in weight loss and maintenance. *American Journal of Clinical Nutrition*. http://doi.org/10.3945/ajcn.114.084038

Levey, A. S., Bosch, J. P., Lewis, J. B., Greene, T., Rogers, N., & Roth, D. (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Annals of Internal Medicine*, *130*(6), 461–470. http://doi.org/10.7326/0003-4819-130-6-199903160-00002

Levey, A. S., de Jong, P. E., Coresh, J., El Nahas, M., Astor, B. C., Matsushita, K., … Eckardt, K.-U. (2011). The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney International*, *80*(1), 17–28. http://doi.org/10.1038/ki.2010.483

Lichtenstein, A. H., Appel, L. J., Brands, M., Carnethon, M., Daniels, S., Franch, H. A., … Wylie-Rosett, J. (2006). Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation*, *114*(1), 82–96. http://doi.org/10.1161/CIRCULATIONAHA.106.176158

Luger, M., Holstein, B., Schindler, K., Kruschitz, R., & Ludvik, B. (2013). Feasibility and efficacy of an isocaloric high-protein vs. standard diet on insulin requirement, body weight and metabolic parameters in patients with type 2 diabetes on insulin therapy. *Experimental and Clinical Endocrinology & Diabetes : Official Journal,*

German Society of Endocrinology [and] German Diabetes Association, *121*(5), 286–94. http://doi.org/10.1055/s-0033-1341472

Lupton, J. R. (2005). *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. *Institute of Medicine of the national academies*.

Luscombe-Marsh, N. D., Noakes, M., Wittert, G. a., Keogh, J. B., Foster, P., & Clifton, P. M. (2005). Carbohydrate-restricted diets high in either monounsaturated fat or protein are equally effective at promoting fat loss and improving blood lipids. *American Journal of Clinical Nutrition*, *81*(4), 762–772.

Marshall, S. J. (2004). Developing countries face double burden of disease. *Bulletin of the World Health Organization*, *82*(7), 556. http://doi.org/10.1590/S0042-96862004000700022

Martin, W., Armstrong, L., & Rodriguez, N. (2005). Dietary protein intake and renal function. *Nutrition & Metabolism*, *2*(1), 25. Retrieved from http://www.nutritionandmetabolism.com/content/2/1/25

Michels, W. M., Grootendorst, D. C., Verduijn, M., Elliott, E. G., Dekker, F. W., & Krediet, R. T. (2010). Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. *Clinical Journal of the American Society of Nephrology*, *5*(6), 1003–1009. http://doi.org/10.2215/CJN.06870909

Misra, A., & Khurana, L. (2009). The metabolic syndrome in South Asians: epidemiology, determinants, and prevention. *Metabolic Syndrome and Related Disorders*, *7*(6), 497–514. http://doi.org/10.1089/met.2009.0024

Müller, M. J., Wang, Z., Heymsfield, S. B., Schautz, B., & Bosy-Westphal, A. (2013). Advances in the understanding of specific metabolic rates of major organs and tissues in humans. *Current Opinion in Clinical Nutrition and Metabolic Care*, *16*(5), 501–8. http://doi.org/10.1097/MCO.0b013e328363bdf9

NIH. (2014). The kidneys and how they work. Retrieved July 3, 2015, from http://www.niddk.nih.gov/health-information/health-topics/Anatomy/kidneys-how-they-work/Documents/yourkidneys_508.pdf

Noakes, M., Keogh, J., Foster, P., & Clifton, P. (2005). Effect of an energy restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional status and markers of cardiovascular health in obese women. *American Journal of Clinical Nutrition*, *81*, 1298–1306.

Paddon-Jones, D., Campbell, W. W., Jacques, P. F., Kritchevsky, S. B., Moore, L. L., Rodriguez, N. R., & van Loon, L. J. (2015). Protein and healthy aging. *American Journal of Clinical Nutrition*. http://doi.org/10.3945/ajcn.114.084061

Patel, V. L., Rogers, R., & Haux, R. (2001). *Medinfo 2001: Proceedings of the 10th World Congress on Medical Informatics, Part 1*. IOS Press. Retrieved from https://books.google.com/books?hl=en&lr=&id=DaBdlWBkvEUC&pgis=1

Pedersen, A. N., Kondrup, J., & Børsheim, E. (2013). Health effects of protein intake in healthy adults: a systematic literature review. *Food & Nutrition Research*, *57*. http://doi.org/10.3402/fnr.v57i0.21245

Phillips, S. M. (2012). Dietary protein requirements and adaptive advantages in athletes. *The British Journal of Nutrition*, *108 Suppl* , S158–67. http://doi.org/10.1017/S0007114512002516

Pimentel, D., & Pimentel, M. (2003). Sustainability of meat-based and plant-based diets and the environment. In *American Journal of Clinical Nutrition* (Vol. 78). http://doi.org/10.1177/0956247808089156

Pomerleau, J., Verdy, M., Garrel, D. R., & Nadeau, M. H. (1993). Effect of protein intake on glycaemic control and renal function in Type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*, *36*(9), 829–834. http://doi.org/10.1007/BF00400358

Popkin, B. M., Horton, S., Kim, S., Mahal, A., & Shuigao, J. (2001). Trends in diet, nutritional status, and diet-related noncommunicable diseases in China and India: the economic costs of the nutrition transition. *Nutrition Reviews*, *59*(12), 379–390. http://doi.org/10.1111/j.1753-4887.2001.tb06967.x

Ravussin, E., Lillioja, S., Knowler, W. C., Christin, L., Freymond, D., Abbott, W. G., ... & Bogardus, C. (1988). Reduced rate of energy expenditure as a risk factor for body-weight gain. *New England Journal of Medicine*, *318*(8), 467–472. Retrieved from http://www.nejm.org/doi/pdf/10.1056/NEJM198802253180802

Roughead, Z. K., Johnson, L. K., Lykken, G. I., & Hunt, J. R. (2003). Controlled high meat diets do not affect calcium retention or indices of bone status in healthy postmenopausal women. *The Journal of Nutrition*, *133*(4), 1020–1026.

Santesso, N., Akl, E. A., Bianchi, M., Mente, A., Mustafa, R., Heels-Ansdell, D., & Schünemann, H. J. (2012). Effects of higher- versus lower-protein diets on health outcomes: a systematic review and meta-analysis. *European Journal of Clinical Nutrition*, *66*(7), 780–8. http://doi.org/10.1038/ejcn.2012.37

Schwingshackl, L., & Hoffmann, G. (2014). Comparison of high vs. normal/low protein diets on renal function in subjects without chronic kidney disease: A systematic review and meta-analysis. *PLoS ONE*, *9*(5). http://doi.org/10.1371/journal.pone.0097656

Senauer, B., & Goetz, L. (2003). The growing middle class in developing countries and the market for high-value food products. Retrieved July 2, 2015, from http://www.researchgate.net/publication/5105128_The_Growing_Middle_Class_in_Developing_Countries_and_the_Market_for_High_Value_Food_Products/file/d912f50ddbb3bcf69e.pdf

Skov, a R., Toubro, S., Bülow, J., Krabbe, K., Parving, H. H., & Astrup, a. (1999). Changes in renal function during weight loss induced by high vs low-protein low-fat diets in overweight subjects. *International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity*, *23*(11), 1170–1177. http://doi.org/10.1038/sj.ijo.0801048

Sterne, J. A. C., Sutton, A. J., Ioannidis, J. P. A., Terrin, N., Jones, D. R., Lau, J., … Higgins, J. P. T. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ (Clinical Research Ed.)*, *343*, d4002. http://doi.org/10.1136/bmj.d4002

Stevens, L. A., Coresh, J., Greene, T., & Levey, A. S. (2006). Assessing kidney function--measured and estimated glomerular filtration rate. *The New England Journal of Medicine*, *354*(23), 2473–83. http://doi.org/10.1056/NEJMra054415

Stevens, L. A., & Levey, A. S. (2005). Measurement of kidney function. *Medical Clinics of North America*. http://doi.org/10.1016/j.mcna.2004.11.009

Szulc, P., Beck, T. J., Marchand, F., & Delmas, P. D. (2005). Low skeletal muscle mass is associated with poor structural parameters of bone and impaired balance in elderly men--the MINOS study. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*, *20*(5), 721–729. http://doi.org/10.1359/JBMR.041230

Tee, E.-S. (2002). Obesity in Asia: prevalence and issues in assessment methodologies. *Asia Pacific Journal of Clinical Nutrition*, *11 Suppl 8*, S694–S701. http://doi.org/369 [pii]

The Cochrane Collaboration. (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. *2011*. http://doi.org/Available from www.cochrane-handbook.org.

Tilman, D., Cassman, K. G., Matson, P. A., Naylor, R., & Polasky, S. (2002). Agricultural sustainability and intensive production practices. *Nature*, *418*(6898), 671–7. http://doi.org/10.1038/nature01014

Traill, W. B., Mazzocchi, M., Shankar, B., & Hallam, D. (2014). Importance of government policies and other influences in transforming global diets. *Nutrition Reviews*, *72*(9), 591–604. http://doi.org/10.1111/nure.12134

Uauy, R., Albala, C., & Kain, J. (2001). Symposium : Obesity in Developing Countries : Biological and Ecological Factors Obesity Trends in Latin America : Transiting from Under- to Overweight 1. *Journal of Nutrition*, (4), 893–899. Retrieved from http://jn.nutrition.org/content/131/3/893S.full.pdf+html

USDA, & DHHS. (2010). *Dietary Guidelines for Americans, 2010. 7th edition*. http://doi.org/10.1016/S0300-7073(05)71075-6

Varadharajan, K. S., Thomas, T., & Kurpad, A. V. (2013). Poverty and the state of nutrition in India. *Asia Pacific Journal of Clinical Nutrition*, *22*(3), 326–39. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23945402

Venkatachalam, M. A., & Rennke, H. G. (1978). The structural and molecular basis of glomerular filtration. *Circulation Research*, *43*(3), 337–347. Retrieved from http://circres.ahajournals.org/content/43/3/337.full.pdf

Wadden, T. A., Foster, G. D., Stunkard, A. J., & Conill, A. M. (1996). Effects of weight cycling on the resting energy expenditure and body composition of obese women. *International Journal of Eating Disorders*, *19*(1), 5–12. http://doi.org/10.1002/(SICI)1098-108X(199601)19:1<5::AID-EAT2>3.0.CO;2-T

Wagner, E. a., Falciglia, G. a., Amlal, H., Levin, L., & Soleimani, M. (2007). Short-Term Exposure to a High-Protein Diet Differentially Affects Glomerular Filtration Rate but Not Acid-Base Balance in Older Compared to Younger Adults. *Journal of the American Dietetic Association*, *107*(8), 1404–1408. http://doi.org/10.1016/j.jada.2007.05.003

Walrand, S., Short, K. R., Bigelow, M. L., Sweatt, A. J., Hutson, S. M., & Nair, K. S. (2008). Functional impact of high protein intake on healthy elderly people, *55905*, 921–928. http://doi.org/10.1152/ajpendo.90536.2008.

WHO. (n.d.). Global and regional food consumption patterns and trends. Retrieved July 2, 2015, from http://www.who.int/nutrition/topics/3_foodconsumption/en/

WHO. (2015). Obesity and overweight. Retrieved July 2, 2015, from http://www.who.int/mediacentre/factsheets/fs311/en/

Wilczynski, N. L., & Haynes, R. B. (2002). Robustness of empirical search strategies for clinical content in MEDLINE. *Proceedings / AMIA ... Annual Symposium. AMIA Symposium*, 904–8. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2244303&tool=pmcentrez&rendertype=abstract

Wolfe, R. R., & Miller, S. L. (2008). The recommended dietary allowance of protein: a misunderstood concept. *JAMA*, *299*(24), 2891–3. http://doi.org/10.1001/jama.299.24.2891

Wycherley, T. P., Brinkworth, G. D., Clifton, P. M., & Noakes, M. (2012). Comparison of the effects of 52 weeks weight loss with either a high-protein or high-carbohydrate diet on body composition and cardiometabolic risk factors in overweight and obese males. *Nutrition and Diabetes*, *2*(8), e40. http://doi.org/10.1038/nutd.2012.11

Wycherley, T. P., Moran, L. J., Clifton, P. M., Noakes, M., & Brinkworth, G. D. (2012). Effects of energy-restricted high-protein, low-fat compared with standard-protein, low-fat diets: a meta-analysis of randomized controlled trials. *The American Journal of Clinical Nutrition*, *96*(6), 1281–98. http://doi.org/10.3945/ajcn.112.044321

Young, V. R., & Pellett, P. L. (1994). Plant proteins in relation to human protein and amino acid nutrition. *The American Journal of Clinical Nutrition*, *59*(5 Suppl), 1203S–1212S.