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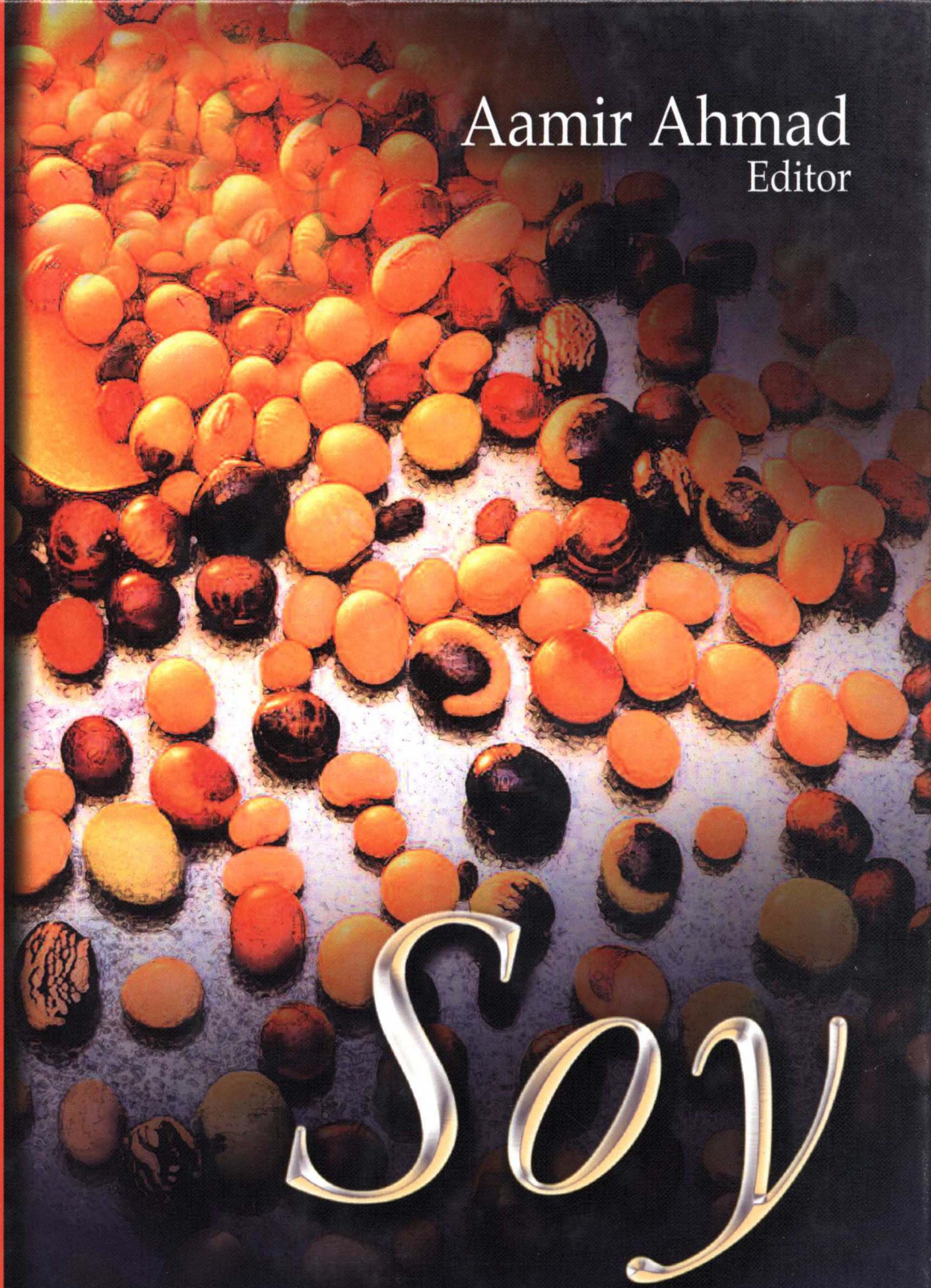

Soy

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SOY

NUTRITION, CONSUMPTION AND HEALTH

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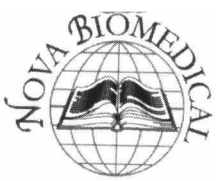

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PREFACE

First of all, I commend Nova Publishers for planning a volume on the health benefits of soy and the constituent compounds. I would also like to take this opportunity to thank the publishing house for entrusting me with managing and editing this book.

This book "*Soy: Nutrition, Consumption and Health*" is a collection of articles (both review and research articles) detailing the very diverse roles of soy-derived compounds. Through a total of 20 chapters, this book showcases the very diverse chemistry, biology and functions of soy. The first ten chapters detail the various reported health beneficial effects of soy and soy-derived compounds. Such effects include cardio-protective, bone health, weight management, anti-hypertensive, anti-atherosclerotic, reducing menopausal symptoms, modulating immune response etc. This is followed by a review of chemistry of soy-derived isoflavones and continues with soy production via tissue culture, its use in baked products, and the use of lactic acid bacteria in increasing the bioavailability and removal of anti-nutritional factors. An article on soy-derived biodiesel fuel adds a new dimension to the many known uses and benefits of soy. In addition to the many health benefits of soy against a number of human diseases, soy-derived compounds have also been investigated for their role in prevention and/or treatment of human cancers. To cover this interesting area of research, this book rounds off with four chapters on the anticancer activity of soy-derived compounds.

This book represents hard work and expertise of researchers from around the globe and I am thankful to all the authors for their invaluable contributions. The very professional conduct of all the contributors and their willingness to adapt their expertise so as to benefit the wider audiences of this book cannot be thanked enough. Last but not the least, I would like to mention my lovely wife, Huma and my angel daughter Nuha for their encouragement, understanding, sacrifice and never ending love.

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Chapter 1

SOY: NUTRITION, CONSUMPTION AND HEART HEALTH

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ABSTRACT

Soyfoods have increased in popularity and number over the last two decades, partly as a result of the US Food and Drug Administration (FDA) permitting a health claim for soy protein that recognises its ability to lower blood cholesterol, first approved in 1999. A similar health claim was granted in the UK in 2002. Interestingly, the increase in soyfoods' popularity has been associated with an increase in controversy. Two main issues will be discussed here. First, the original health claim has been challenged based on the results of human clinical studies conducted after the date of approval. The rationale for the challenge was summed up in a report compiled by the American Heart Association. Their Soy Advisory publication concluded that in studies after 1999, soy protein only modestly lowered low density lipoprotein (LDL)-cholesterol (C)and did not exhibit a dose-response effect. Second, the increased consumption of soy has led to greater scrutiny of soy phytochemicals, and there has been some debate as to whether the cholesterol lowering activity of soy protein is attributable to the naturally occurring isoflavone content, or other mechanisms.

Numerous randomized clinical trials (RCTs) have been conducted with soy protein (with and without isoflavones) and soy isoflavones alone since 1999. Data from these studies have been pooled and a number of meta-analyses have been conducted since the original analysis published by Anderson in 1995. In the main these analyses have assessed the effects of soy protein on lipid levels, in particular LDL-C. These meta-analyses are reviewed in this chapter with the aim of evaluating the importance of factors

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such as isoflavone content, protein intake, baseline cholesterol concentration and various other factors on the lipid-altering effects of soyfoods consumption. Despite employing varying inclusion criteria, these analyses consistently report a reduction in LDL-C of ~0.2 mmol/L, equivalent to a reduction of 4.5 to 7.0%. Also, high-density lipoprotein cholesterol (HDL-C) is typically increased by 0.1-0.4 mmol/L and blood triglycerides (TAG) reduced by 0.10 mmol/L. RCTs published since 1999 have furthermore been reviewed with reference to detailed quality criteria in order to assess the magnitude of the effect reported in recent studies. Twenty-seven studies with 37 treatment arms a median intake of 25 g soy protein/day, and representing 2122 volunteers were identified and data were pooled to conduct a further meta-analysis specifically to address the extent of the effects of soyfoods on blood lipids post-1999. The results of this analysis indicate that LDL-C was reduced by 0.22 mmol/L - not dissimilar to the effects reported in other reported meta-analyses. In addition, HDL-C was increased significantly by 0.08 mmol/L - equivalent to an increase of 5%. The findings of the present analysis, and others published in the last decade, suggest that isoflavones *per se* are not instrumental in the lipid-altering effects of soyfoods. Plausible mechanisms that may responsible for the cholesterol reducing properties of soy protein will also be discussed. In addition areas for future research and public health implications will be highlighted.

INTRODUCTION

Soya beans and foods prepared from them have been integral part of Asian diets for centuries and over the last two decades have increased in significance in Western diets. The increase in popularity and availability of soyfoods in the West was prompted, in part, as a result of the US Food and Drug Administration (FDA) in 1999 permitting a health claim for soy protein that recognises its ability to lower blood cholesterol [1]. A similar health claim was granted in the UK in 2002 [2].

Soy protein is the protein component derived from the legume - soybean - Glycine max and is present in a wide range of soyfood products; it is largely comprised of storage protein with the two main types being β conglycinin (7S globulin) and glycinin (11S globulin). All soybean-derived protein foods naturally contain isoflavones [3-4]. Isoflavones are a subgroup of flavonoids. Soy is by far the richest source of isoflavones, however small amounts are also found in other legumes and pulses such as chickpeas, fava beans, pistachios and peanuts, as well as some other fruits and nuts. Isoflavones are intrinsic plant compounds that occur largely as glycosidic conjugates, which are hydrophilic and unable to partition into the lipophilic oil found in the bean and thus naturally associate with protein. The content and form of the isoflavones in the soybean protein is dependent on many factors including growing conditions, its genetic variety, the nature of the process used to extract the protein and how the soy food is prepared. Genistein, daidzein and glycitein are the specific isoflavones found in soy protein and represent 55-65%, 35-45% and 5-10% of the total respectively [4].

Many of the health-promoting properties of soyfoods have been attributed to the isoflavone content of soy protein, although with respect to cholesterol-reduction there is growing evidence to suggest that it is the protein per se that is of key importance and that isoflavones play a minor role, at most, in this regard.

People consume soyfoods for a variety of reasons. Many consumers purchase them as a vegetarian or vegan alternative to meat; others will purchase dairy-alternative products, such

as soymilk and yoghurts, as an alternative to cow's milk because they suffer from an allergy to milk protein or are lactose intolerant. Others select soyfoods as a sustainable and eco-friendly source of protein or may wish to consume soy protein as a dietary strategy to help manage blood cholesterol. Finally there are those who prefer soy because they simply believe that soy is good for them, or they are socially accustomed to, soyfoods. While it is irrefutable that soyfoods are lactose-free, free from milk protein and suitable for vegetarians, the increase in soyfoods' popularity has been associated with an increase in controversy, specifically with regard to the extent that soy protein reduces cholesterol.

The rationale for the challenge was summed up in a report compiled by the American Heart Association in their Soy Advisory publication, which concluded that in studies after 1999, soy protein only modestly lowered LDL-C and did not exhibit a dose-response effect [5]. The original health claim for soy protein and cholesterol lowering was granted in 1999, now over a decade ago, and since that time many further human clinical studies have been published. It should also be recalled that prior to the claim being granted, over two decades of peer-reviewed evidence from the scientific literature was evaluated for the health claim petition to the FDA and the claim was granted as a result of this review.

The body of scientific evidence was also summarized by Anderson and colleagues in the first meta-analysis of the literature in 1995 assessing the effect of soy protein on plasma total- and LDL-C [6]. Since that time additional meta-analyses have been published that consider this relationship [7-16].

A nomogram was developed by Sirtori *et al.* [17] which permitted a prediction of the approximate cholesterol reduction with soy protein based on the initial baseline cholesterol concentrations of a study cohort. This nomogram provided a likely explanation for the differences in the results from the more recent meta-analyses versus the one published by Anderson *et al.* [1], since the studies included in the latter included subjects with higher mean baseline cholesterol levels. RCTs conducted with soy protein after the 1995 Anderson meta-analysis tended to use cohorts with lower plasma cholesterol.

In this chapter publications since 1999 are reviewed in order to assess the overall magnitude of the effect of soy protein on cholesterol reduction and factors that may be influential in determining the extent to which soy protein can exert this effect. The importance of factors such as isoflavone content, protein intake, baseline cholesterol level and other factors will be also be assessed.

The focus of health claims for soy protein is on the modification of total- and LDL-C. This is because authoritative bodies around the world that approve health claims accept these as surrogate biomarkers of cardiovascular disease risk - see for example the EFSA guidance [18]. Other lipid-associated parameters are associated with cardiovascular disease risk, such as triglycerides (TAG), non-HDL-C, apolipoprotein (Apo) B, HDL-C (inversely) and Apo AI (inversely). As yet, these have not been universally accepted by regulatory authorities as cardiovascular risk biomarkers that can be used to develop disease risk reduction claims; nonetheless changes in these parameters can provide supportive evidence.

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METHODS

Identification and Selection of Trials

Two main searches were conducted to identify either meta-analyses or RCTs that evaluated soy protein intake and the effect on a measure of blood lipids; LDL-C was considered the primary outcome measure for the reasons outlined in the Introduction.

The first search was conducted in Medline and in the Cochrane library in Sept 2011 to identify published meta-analyses; the primary search terms were soy(a) + cholesterol (or blood lipids) + meta-analyses, the search was confined to title and abstract.

The second search also conducted in Medline and in the Cochrane library used, soy(a) + cholesterol (or blood lipids) as the primary search terms; the search was date restricted to those studies published between 1999 to 2011 (through October 2011) and was restricted to human clinical studies. Searches were de-duplicated and consolidated. Further hand searches of reference lists of identified meta-analyses and reviews were made. References were sorted by alphabetical order of the first author and any studies cited in the original FDA report excluded.

The suitability of the studies for further review was then assessed by the application of detailed inclusion and exclusion criteria. Broadly, RCTs with crossover or parallel designs comparing healthy volunteers (not taking lipid-lowering medication) consuming soy protein with those consuming a suitable non-soy, protein-containing control were identified. Studies where combinations of soy constituents were given as the treatment, for example soy lecithin and soy protein, were excluded, as were studies using food combinations such as soy protein with soluble fibre, plant stanols and/or sterols, nuts, etc. Studies where the primary outcome measure was not related to blood lipids were excluded, unless it was clear that they were adequately statistically powered to assess blood lipids. Also excluded were studies in populations with chronic diseases, obesity (body mass index > 30 kg/ m^2) or where there was >2 kg average weight loss during the trial.

In brief, a trial was included if an original RCT, with a parallel or crossover design, published in a peer reviewed journal in English and included a suitable (protein-based, non-soy) control treatment and measured blood lipids.

The permitted range of soy protein intake was 10-40 g per day and could be derived from isolated soy protein (ISP), soy protein concentrates, or soya foods; the control treatment needed to have a similar macronutrient content and volunteers were healthy or mildly hypercholesterolaemic adults or those with diabetes controlled by dietary intervention only. Study duration was required to be a minimum of four weeks or one menstrual cycle.

Data Extraction

From identified studies data were extracted and the key characteristics from RCTs collated, including design (parallel or crossover), whether blinded, number of volunteers, gender, age, location, duration of study, source and amount of soy protein, blood lipid values, statistical analysis and, where available, macronutrient content of diet.

Statistical Treatment of Data

Means and standard deviations (SD) for the changes from baseline in blood lipid values were calculated for intervention and control treatments. In brief for parallel studies, baseline (after randomisation) start of study blood lipid values were subtracted from end of study values for the control and intervention treatment(s). The mean resulting control and treatment differences in blood lipid values were compared. This correction for baseline values allowed for any non-treatment related drift in blood cholesterol to be taken into account.

In crossover studies, where possible the above procedure was followed, or alternatively, end of control and intervention period values for blood lipid were compared. Where individual SD or standard error (SE) of the mean difference in blood lipids values were not reported these were computed as the average of baseline and end-of-study values, or where no suitable data were available, the mean value from the dataset as a whole was ascribed to the study.

Weighted estimates of trial results were combined with a fixed effect approach and 95% confidence intervals (CIs) were calculated and heterogeneity tested. To pool the overall standardised mean effect size, each study was weighted by the reciprocal of the total variance for change in blood lipid levels.

Additionally, meta-regression analysis was conducted with no intercept term to evaluate the dose-response between soy protein or isoflavones/g soy protein and net change in either LDL-C or HDL-C, weighting by the inverse of the variance. Comprehensive Meta Analysis software (Biostat, Englewood, NJ 07631, USA) was used for all statistical analysis.

To examine the effect on various predictors of response, sub-analyses were conducted to explore the effect of study design, source of protein and gender on the standardised mean difference in lipid responses. To examine potential publication bias the SE of the studies were plotted against their corresponding effect size and plotted as funnel plots.

RESULTS

The search identified 14 meta-analyses, two of these were conducted with extracted soy isoflavone studies [19-20] and 10 related to soy protein with or without soy isoflavones [7-16], one to a review and nomogram [17] and, one was not relevant as it related to non-soy legume consumption [21]. Data from the 10 relevant meta-analyses were extracted in a common format and are summarised in Table 1.

Commentary Related to Meta-Analyses Protein Intake

The average soy protein intake in the meta-analyses conducted up until 2005 was typically 40 g or greater per day. Whereas in the more recent analysis of Harland [13], studies with intake of >40 g/day were not considered for further analysis. The rationale adopted was that higher levels of protein intake are not practically achievable on a daily basis and are well in excess of the amount of soy protein required to satisfy the permitted FDA claim. Furthermore such high protein intakes were likely to substantially affect overall

macronutrient intake, recognizing that 40 g is typically 40% of the average adult male protein intake and 50% of the average adult female intake. A lower median intake of 30 g, was also reported in the most recent meta-analysis of Anderson [16]. No dose response relationship has been found between practical soy protein intakes (12-40 g soy protein/day) and blood lipid modification [13].

However, in meta-analyses where studies with higher protein intakes (>40 g/day) were retained in the analysis, meta-regression showed a dose-response relation between soy protein and isoflavone supplementation and net changes in blood lipids [7]. It has been previously suggested that 25 g/day "soy protein" is not the minimum effective level, but there currently is insufficient data available at levels of intake of less than 25 g protein to establish a lower "threshold" level or whether soy protein shows cholesterol lowering efficacy below 25 g/day [22]. More recently it has been suggested that the minimum effective dose is equivalent to *ca* 12g soy protein/day [23]. However, there remains a paucity of data from RCTs where the intervention has involved ≤15g/day and hence the minimum effective dose is an aspect that requires further investigation.

LDL-C reduction

All of the published meta-analyses report a value for the reduction in LDL-C. This reduction in LDL-C was significant in the total group of retained studies in all but one analysis [8]. The stated objective of this analysis by Weggemans *et al.* [8] was to assess the contribution of isoflavones and the number of retained studies in this meta-analysis is smaller than for the other meta-analyses, in these respects it is not directly comparable to other analyses [6-7, 11, 13, 24], where the primary objective was to assess the effect of soy protein on blood lipids.

The meta-analyses published during the last decade have provided point estimates for the reduction in LDL-C of 0.11-0.25 mmol/L, which is just under half the reduction reported in the original Anderson meta-analysis of 0.56 mmol/L [6]. Using regression analysis, Anderson estimated that 25g/day "soy protein" would result in a decrease in Total-C of 0.23 mmol/L, while concluding that there is no specific dose response effect.

Impact of Baseline Cholesterol

With respect to importance of baseline cholesterol, three analyses found baseline cholesterol level had no impact [5, 8, 10], while the findings from four other meta-analyses suggest that cholesterol reduction may be somewhat greater in those with higher baseline cholesterol [7, 9, 11-12]. Sirtori has argued, by reference to a nomogram, that the cholesterol response can indeed be predicted using a non-linear model and is far more pronounced in individuals with the highest cholesterolemia [17]. The nonlinear nature of the dependence of cholesterol reduction by soy protein on baseline cholesterol may explain why some meta-analyses do not show a correlation as the study cohorts selected have lower cholesterol levels, putting them in the relatively linear and flat portion of the dose-response curve. However, there are number of fundamental differences between the selection criteria adopted by Anderson and those of other researchers. For example, Anderson included those with familial

hypercholesterolemia, subjects on lipid-lowering medication and those with severely elevated baseline cholesterol. The criteria adopted by Balk *et al.* [10] in their 2005 analysis allowed a large number of studies to be included; the rationale adopted by these researchers allowed sub-analysis to be carried out to determine the effect of key variables. However in the Balk *et al.* analysis, there is not always clear differentiation between studies with isoflavone supplements, soy protein with and without isoflavones and other sources of soy protein, and also included studies in those with chronic conditions including diabetes, metabolic syndrome, familial hypercholesterolaemia and pre-diagnosed heart conditions.

Intrinsic and Extrinsic Effects of Soy Protein

The inclusion criteria adopted by Jenkins *et al.* in their 2010 meta-analyses [15] make reference to information from the AHA Soy Advisory review [5], Anderson [6] and NHANES III population survey data. These authors interrogated the data to estimate "the intrinsic effect of soy protein" on LDL-C (that related to the soy protein *per se*) and the extrinsic (displacement) potential of soy in replacing saturated fat and other components in the diet associated with elevated blood lipids. Their objective was to re-evaluate the studies identified in the AHA Soy Advisory review [5] and to apply a rigorous statistical analysis to determine whether the heart health claim for soy continues to be justified [24].

The intrinsic effect of soy to lower plasma cholesterol was derived from a meta-analysis of 11 RCTs where macronutrient profiles of both soy protein and protein control diets were balanced (see Table 1). The results from this meta-analysis indicated a mean LDL-C reduction of 0.17 mmol/L ($n = 22$; $P< 0.0001$) or 4.3% for soy which could be attributable to the soy protein itself and not due to any other dietary factor. Jenkins *et al.* (2010) then further explored the proposed "extrinsic" effect of soy protein in displacing foods higher in saturated fat and cholesterol using the standard predictive equations for LDL-C [25] based on the isocaloric substitution of a range of 13–58 g/d soy protein containing foods for animal protein foods, e.g., cow's milk, yogurt and meat. The estimated displacement value of soy (in the range, 13–58 g/d) using typical American diets (50% percentile NHANES III intake data) was a 3.6–6.0% reduction in LDL-C, due to displacement of saturated fats and cholesterol from animal foods. The total LDL-C reduction attributable to the combined intrinsic and extrinsic effects of soy protein foods therefore ranged from 7.9 to 10.3% [24].

Quality Assessment of Studies

Detailed quality ratings of the studies was undertaken by Anderson in the most recent meta-analysis [16]. A 24-point scale was developed which assessed 12 aspects of study quality including subject selection, randomization, blinding, therapeutic intervention description, study design, non completing subjects description, subject completion rates, appropriate measurement of lipid outcomes, weight assessment, data analyses, reporting of adverse effects and study funding information. A sub-group analysis was conducted in which the 9 interventions with higher grades (score >14) were compared with 8 studies with lower grades (score <9). Despite marked differences in quality assessment the variance-weighted changes were not significantly different; mean changes in LDL-C with soy protein

consumption were -0.22 mmol/L (95% CI, -0.31 to -0.12) for higher and -0.15 mmol/dl (95% CI, -0.25 to -0.05) for lower grade studies respectively. All the identified meta-analyses in this chapter have varied study selection criteria, yet despite this variation in inclusion criteria there is a remarkable consistency in the reporting of a significant reduction in LDL-C of ~0.2mmol/L, equivalent to 4-7% reduction compared to baseline.

Effects on HDL-C and TAG

Results from meta-analyses suggest that soy protein interventions result in small increases in HDL-C levels of 0.01-0.04 mmol/L, which are not consistently statistically significant, although some of the more recent meta-analyses report larger and statistically significant increases [7, 11, 13]. By reference to 29 intervention arms from parallel-design studies, net HDL-C values were reported to be 0.044 mmol/L (95% CI, 0.014 to 0.074) higher, equivalent to an increase of 3.2% ($P<0.007$) in soy protein diets compared to control in the most recent meta-analysis [16]. It has also been suggested that the increase in HDL-C is greater not only in parallel studies, but also in longer interventions and in subjects with higher baseline cholesterol (Total-C >6.2mmol/L) [7].

Fewer studies report the effect of soy protein on TAG levels, however typical reductions of ~0.10 mmol/L are achieved, which are usually statistically significant ($P<0.05$). A higher reduction in TAG levels was reported by the recent Anderson meta-analysis in which 27 parallel interventions including 888 control and 860 soy-treated subjects resulted in changes in TAG of -0.17 mmol/L (95% CI, -0.25 to -0.08) ($P<0.008$), which represents a mean reduction of 10.7% [16].

Role of Isoflavones

The meta-analyses of Taku suggest that a minimal contribution to blood cholesterol reduction is made by isoflavones themselves [12, 20]. For example, soy protein with isoflavones reduced LDL-C by 0.18 mmol/L, whereas soy protein depleted of isoflavones reduced LDL-C by 0.13 mmol/L, a difference of 0.05 mmol/L [12]. Extracted soy isoflavones minimally reduced LDL-C by 0.03 mmol/L which was non-significant [20]. Other analyses were unable to demonstrate that isolated isoflavones had a cholesterol lowering effect in their own right [8-9], suggesting that isoflavones per se are not the causal agent for cholesterol-lowering property of soy protein. Indeed two meta-analyses conducted with isoflavones alone demonstrate only a trivial effect on LDL-C of 0.00-0.03 mmol/L [19-20]. Clinical studies conducted more recently that have not been included in the previous meta-analyses of isolated isoflavones consistently fail to show a significant lowering of LDL-C by isolated isoflavones [26-31]. It has been argued that isoflavones must play a role in the cholesterol lowering property of soy protein since soy protein depleted of isoflavones does not have as potent an effect as soy protein containing its' naturally occurring isoflavones. Depleting soy protein of isoflavones by the typical method of alcohol-washing not only removes isoflavones but other phytochemicals and micronutrients associated with soy protein, as well as many smaller molecular weight proteins or peptides [32].

Furthermore, alcohol-washing denatures soy protein, which may impact the digestibility and bioavailability of soy peptides in the digestive tract. Consequently, the analysis of low isoflavone soy proteins compared to standard soy proteins may actually be measuring an effect due to the absence of low molecular weight soy protein bioactives, rather than isoflavones absence *per se*.

IDENTIFIED RCTS FOR THE CURRENT META-ANALYSES

The search identified 117 RCTs from the period 1999 to date October 2011. After applying the detailed inclusion and exclusion criteria described in the Methods, 27 studies representing 2122 subjects and 37 treatment arms were retained for further analysis. Details of these studies are shown in Table 2, which also includes two retained studies for which numerical data was unavailable.

Of the 27 studies, 11 were parallel-design and 16 crossover studies. Studies were conducted in pre- and postmenopausal women and men for a minimum of four and up to 104 weeks, the median intake was 25 g/day and the isoflavone content of the soy protein was in the range 1.0 - 9.3 mg aglycone equivalent/g soy protein. Absolute isoflavone intake was in the range 24 - 132 mg aglycone equivalent/day. Studies were retained where the macronutrient of the supplementary protein-rich soybean component included either as a sachet of powder (ISP) or a food specially manufactured for the study, and a control product that was reported to be identical or very close in macronutrient composition. Where foods were prepared from ISP or other soy protein-rich concentrates they were designated SP and included yoghurt-like desserts, milks and muffins; where whole soyfoods were used in the studies these were designated SyF and included tofu, soynuts, soy flour and soy milk. Milk proteins or casein were the main sources of control animal-derived protein in the majority of cases, but meat proteins were used in four studies [33-36].

Effect on Primary Outcome LDL-C

The standard difference in mean LDL-C for all studies was -0.22 mmol/L (95% CI, -0.283 to -0.149), which was highly statistically significant ($P<0.0001$) and equivalent to a reduction compared to baseline of 5.5%. Two studies were retained where subjects were identified as being either at increased cardiovascular risk from the metabolic syndrome [34], or had diabetes controlled by diet alone [37]. In a further study, four subjects revealed they were on medication after completion of the study, however separate analysis by the authors indicated these subjects did not respond differently to the group as a whole [38]. LDL-C data were pooled excluding these three studies (four treatment arms) and the standard difference in mean LDL-C, was not markedly different in this case at -0.20 mmol/L (95%CI, -0.269 to -0.129), ($P<0.0001$). Heterogeneity was not evident in the dataset. Because study selection in our analysis aimed to ensure that macronutrient intakes were similar, it was anticipated that the mean difference reported would be similar to that reported by Jenkins *et al* in his 11 macronutrient matched studies, where the reduction in LDL-C was 0.18 mmol/L [15]. Analysis by sub group indicated that standard difference in mean LDL-C for studies using

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