The effects of almond consumption on fasting blood lipid levels: a systematic review and meta-analysis of randomised controlled trials

Kathy Musa-Veloso*, Lina Paulionis, Theresa Poon and Han Youl Lee
Intertek Scientific and Regulatory Consultancy, 2233 Argentia Road, Suite 201, Mississauga, Ontario, L5N 2X7, Canada

Abstract
A systematic review and meta-analysis of randomised controlled trials was undertaken to determine the effects of almond consumption on blood lipid levels, namely total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), TAG and the ratios of TC:HDL-C and LDL-C:HDL-C. Following a comprehensive search of the scientific literature, a total of eighteen relevant publications and twenty-seven almond-control datasets were identified. Across the studies, the mean differences in the effect for each blood lipid parameter (i.e. the control-adjusted values) were pooled in a meta-analysis using a random-effects model. It was determined that TC, LDL-C and TAG were significantly reduced by −0.153 mmol/l (P < 0.001), −0.124 mmol/l (P = 0.001) and −0.067 mmol/l (P = 0.042), respectively, and that HDL-C was not affected (−0.017 mmol/l; P = 0.207). These results are aligned with data from prospective observational studies and a recent large-scale intervention study in which it was demonstrated that the consumption of nuts reduces the risk of heart disease. The consumption of nuts as part of a healthy diet should be encouraged to help in the maintenance of healthy blood lipid levels and to reduce the risk of heart disease.

Key words: Almonds; Blood lipids; Cholesterol; TAG

Almonds are nutritionally dense(1). According to compositional data from the United States Department of Agriculture, 100 g of raw, unroasted almonds provides 2423 kJ (579 kcal), 50 g of fat, 13 g of insoluble dietary fibre and 21 g of protein(2). There is some natural variability in the composition of almonds in terms of the fat and fatty acid contents; when expressed on a per 100 g basis, almonds contain about 45 to 54 g of fat, with relative amounts of PUFA, MUFA and SFA of 9 to 15, 25 to 36, and 3 to 5 g, respectively(3). In addition, almonds contain small amounts of plant sterols(3–5), and are sources or high sources of several minerals and vitamins (i.e. Ca, Fe, Mg, P, K, Zn, Cu, Mg, thiamin, riboflavin, niacin and vitamin E), according to the requirements for nutrition claims, as set out in Regulation EC 1924/2006(6).

Several of the compositional attributes of almonds are ideal for the maintenance of healthy blood lipid levels. Indeed, in a meta-analysis of randomised controlled trials, Phung et al.(7) reported that almond consumption was associated with a significant reduction in total cholesterol (TC) (−0.18 mmol/l; 95% CI −0.34, −0.02 mmol/l), as well as a strong trend toward a reduction in LDL-cholesterol (LDL-C) (−0.15 mmol/l; 95% CI −0.29, 0.00 mmol/l). No effects on HDL-cholesterol (HDL-C), TAG, or on the ratio of LDL-C:HDL-C were observed. The meta-analysis by Phung et al.(7) was based on five randomised controlled studies (representing a total of 142 participants). More than 7 years have elapsed since Phung et al.(7) conducted their literature search; thus, all randomised controlled trials that have since been published were identified, and, using the totality of evidence, the effects of almonds on blood lipid levels were re-evaluated.

Abbreviations: CAD, coronary artery disease; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; T2DM, type 2 diabetes mellitus; TC, total cholesterol.

* Corresponding author: K. Musa-Veloso, fax +1 905 542 1011, email kathy.musa-veloso@intertek.com

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Methods

Literature search

The systematic review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

In May 2013, the electronic search tool Dialog™ was used to search eight literature databases (Allied & Complementary Medicine™, Adis Clinical Trials Insight, CAB Abstracts, Elsevier Biobase, EMBASE®, Foodline™, Science, Medline®, and National Technical Information Service). Dialog™ was subsequently replaced by ProQuest Dialog™, which did not index one of the eight original literature databases that were searched (i.e. Elsevier Biobase). Updated literature searches were conducted in May 2014 and in February 2015, using ProQuest Dialog™ to access seven of the eight original databases.

The search terms used reflected the exposure (‘almond’, ‘Prunus amygdalus’, ‘P. amygdalus’, ‘Prunus dulcis’, ‘P. dulcis’) and the study population (‘human’, ‘subject’, ‘participant’, ‘volunteer’, ‘patient’, ‘elder’, ‘senior’, ‘geriatric’, ‘adult’, ‘men’, ‘women’, ‘man’, ‘woman’, ‘teen’, ‘adolescent’, ‘people’, ‘person’, ‘individual’), and were required to appear in the titles or abstracts of the articles. The literature searches were restricted to studies conducted in humans; that is, the keywords used to limit the searches to human studies (‘animal’, ‘rodent’, ‘rat’, ‘mouse’, ‘mice’, ‘dog’, ‘pig’, ‘rabbit’, ‘hamster’, ‘monkey’, ‘in vivo’, ‘ex vivo’) were required not to appear in the descriptor or subject field of the records. No restrictions with respect to the health outcomes of interest or language were imposed on any of the literature searches. As well, no restriction on the year of publication was imposed on the first literature search.

Inclusion/exclusion criteria

The following inclusion criteria were applied: (1) a human intervention study that was randomised and controlled (such that the control group/phase could have consisted of either no food or any food(s) without tree nuts or fractions of tree nuts); (2) a full-length article that was published in a peer-reviewed journal; (3) the objective of the study (either primary or secondary) was to assess the effects of almond consumption on blood lipid levels; (4) the amount of almonds consumed was reported; (5) the subjects were adults (aged ≥18 years of age) without serious disease such as heart disease; (6) the study duration was ≥4 weeks; (7) fasting blood lipids (i.e. TC, LDL-C, HDL-C, TAG; TC:HDL-C; LDL-C:HDL-C), dietary interventions (dose, form of almonds, provision of foods or meals, duration, frequency of intake, pattern of intake), background diets and macronutrient intakes, statistical results, and the mean difference in the effect for each blood lipid parameter (see the Statistical analysis section for details on how the mean difference in the effect was calculated for the crossover and parallel studies).

Health Canada’s standardised quality appraisal tool was used to determine the quality of the studies. A quantitative score (zero or one) was assigned to each of the fifteen items included in the tool, and studies with scores of ≥8/15 were considered to be ‘higher quality’ while studies with scores of ≤7/15 were considered to be ‘lower quality’. Study quality was appraised by one reviewer (L. P.).

Statistical analysis

Several of the identified studies had multiple comparisons (e.g. one study may have had three arms, including one control and two different almond doses). Each almond-control comparison, hereinafter referred to as a stratum, was considered a separate trial; however, the control sample size was divided evenly amongst the comparisons so as to avoid inflating the weight of each stratum. For parallel studies, the mean difference in the effect for each blood lipid parameter was calculated as the change from baseline in the control group subtracted from the change from baseline in the almond group. For crossover studies, the mean difference in the effect for each blood lipid parameter was calculated as the blood lipid value at the end of the control phase subtracted from the blood lipid value at the end of the almond phase.

In order to determine the effects of almonds on each of the blood lipid parameters, the results of the studies were pooled in a meta-analysis, with the mean difference in the effect and the inverse of the variance used as the weighting factor. In the majority of the studies, variances for the mean differences were not reported; thus, variances were calculated using information provided in the publication (e.g. using CI or individual variances for the almond and control groups). If, in parallel
studies, variances for the changes from baseline were reported separately for the almond and control groups, then a pooled variance for the mean difference was calculated. If, for parallel studies, variances only for the baseline and end of treatment values were reported, then these were used to calculate the variance for the change from baseline, using a correlation coefficient of 0.8. Similarly, for crossover studies, if variances only for the end of treatment values were reported, then the variance for the mean difference was calculated using a correlation coefficient of 0.8. A correlation coefficient of 0.8 was used because this value approximated that calculated from the studies in which variances were provided for the baseline, end of treatment, and change from baseline measures. A random-effects model was used, according to the methods described by DerSimonian & Laird, given that random-effects models take into consideration the variability in response both within and between studies.

The pooled estimates and accompanying 95% CI were determined using Comprehensive Meta-analysis Software (version 2.2.064). Publication bias was assessed according to the trim-and-fill method developed by Duval & Tweedie. With this method, asymmetry in the funnel plot is searched for. If the asymmetry is determined to be due to the presence of small studies (with large variances) in which large effect sizes were reported, with an unbalanced number of small studies, variances only for the end of treatment values were reported, then the asymmetry was determined using Comprehensive Meta-analysis Software (version 2.2.064). Publication bias was assessed according to the method developed by Duval & Tweedie.

Subgroup analyses were conducted to evaluate the influence of dose (i.e. <45 g/d, 45–60 g/d, ≥60 g/d), study design (i.e. parallel or crossover), the control food/diet (i.e. whether it was provided or if subjects were simply instructed to avoid nuts), the duration of the study (i.e. ≥12 weeks v. 4 to <12 weeks), and of baseline blood lipid level. Baseline blood lipid levels were categorised dichotomously as ’optimal’ or ’not optimal’, based on the targets established in the National Cholesterol Education Program Adult Treatment Panel III guidelines (i.e. optimal blood lipid levels were defined as: LDL-C < 2.59 mmol/l; HDL-C ≥ 1.03 mmol/l; TAG < 1.69 mmol/l). For crossover studies, the categorisation was based on the reported baseline lipid level; for parallel studies, the categorisation was based on the average of the baseline lipid levels that were reported for each group, weighted by the sample size of each group. Subgroup analyses were conducted when there were at least three strata available for pooling.

Results

Literature search results and overview of included studies

The three literature searches resulted in the identification of 1697 titles, of which eighteen publications met all of the inclusion criteria and none of the exclusion criteria (Fig. 1).

The eighteen publications provided a total of twenty-seven strata (Table 1). Of the twenty-seven strata, seventeen were from parallel trials, and the remaining ten strata were from crossover trials. The number of study completers ranged from thirteen to 137 amongst the eighteen publications. Both male and female subjects were studied in the majority of the strata, with the exception of three strata wherein only females were studied (Abazarfard et al.; Kurlandsky & Stote strata 1 and 2). The subjects were described by the authors as generally healthy in seven strata (Abazarfard et al.; Berryman et al.; Foster et al.; Kurlandsky & Stote strata 1 and 2; Spiller et al. strata 1 and 2), generally healthy but habitual smokers in two strata (Jia et al. strata 1 and 2), generally healthy or hyperlipidaemic in two strata (Sabaté et al. strata 1 and 2), hyperlipidaemic in four strata (Damasceno et al.; Jenkins et al. strata 1 and 2; Tamizifar et al.), pre-diabetic or at risk of type 2 diabetes mellitus (T2DM) in five strata (Tan & Mattes strata 1 to 4; Wien et al.). In the remaining seven strata, medicated subjects were studied, including subjects with T2DM on oral hypoglycaemic therapy (Sweazea et al.; Cohen & Johnston), or pre-diabetic or at risk of type 2 diabetes mellitus (T2DM) in five strata (Tan & Mattes strata 1 to 4; Wien et al.).

Almond interventions

Across all strata, the average daily intake of almonds ranged from 20 to 113 g/d, and the duration of the almond consumption period ranged from 4 weeks to 18 months. Almonds were required to be consumed every day in all studies except two, in which 28 g (1 oz) of almonds were required to be consumed 5 days per week or 43 g (1.5 oz) of almonds were required to be consumed five to seven times weekly.

Whole, raw (unblanched, unsalted) almonds were consumed in nine strata (Abazarfard et al.; Berryman et al.; Damasceno et al.; Jenkins et al. strata 1 and 2; Ruisinger et al.; Spiller et al. strata 1 and 2; Wien et al.). In five strata (Cohen & Johnston; Tan & Mattes strata 1 to 4), the almonds that were consumed by the subjects were not specifically described by the study authors as raw, unblanched almonds; however, based on the reported energy value of the almonds, it was determined that the almonds were most probably raw, unblanched almonds. A variety of almonds, namely whole (raw), roasted, and flavoured almonds were consumed in one stratum (Foster et al.; dry, roasted almonds were consumed in one stratum (Wien et al.); and almond powder was consumed in one stratum (Tamizifar et al.). The types of almonds used were not specified in two strata (Kurlandsky & Stote strata 1 and 2). In eight strata, all meals and snacks were provided and the almonds were said to have been consumed as a snack (Berryman et al.) or incorporated into the meals and snacks (Jia et al. strata 1 and 2; Li et al.; Lovejoy et al. strata 1 and 2; Sabaté et al. strata 1 and 2). The form of almonds that was used was described only by Berryman et al., who reported administering unsalted, whole, natural almonds with skins, and by Jia et al. strata 1 and 2, who reported using almond powder. In the remaining five strata in which all meals and snacks were provided (Li et al.; Lovejoy et al. strata 1 and 2; Sabaté et al. strata 1 and 2), it is assumed that whole
almonds, almond pieces and ground almonds were used to prepare the meals.

**Control foods/diets**

Although all studies were randomised and controlled, the control food was not defined in some studies but defined in other studies. In thirteen of the twenty-seven strata, subjects in the control group or during the control phase were instructed not to consume nuts, but were not provided with a control food or with a control diet (Abazarfard et al. (9); Swazey et al. (10); Foster et al. (16); Kurlandsky & Stote strata 1 and 2 (14); Ruisinger et al. (27); Tamizifar et al. (21); Tan & Mattes strata 1 to 4 (22); Wien et al. (23)). In fourteen strata, either a 'control food' (e.g. cheese sticks or a muffin or olive oil) was provided (Cohen & Johnston (24); Damasceno et al. (19); Jenkins et al. strata 1 and 2 (20); Spiller et al. strata 1 and 2 (17)), or the entire control diet was provided (Berryman et al. (11); Jia et al. strata 1 and 2 (13); Li et al. (20); Lovejoy et al. strata 1 and 2 (26); Sabaté et al. strata 1 and 2 (18)).

**Effects of almonds on fasting blood lipids**

The fasting blood lipids that were assessed in each of the twenty-seven strata, as well as other information pertinent to the subgroup analyses (i.e. study design, almond intake, whether a control food/diet was provided, study duration, and baseline blood lipid levels), are summarised in Table 2. In the study by Lovejoy et al. strata 1 and 2 (26), baseline TAG levels were not reported; thus, a determination as to

**Study quality**

Based on Health Canada’s quality appraisal tool, all of the studies were considered to be ‘higher quality’ (8). Across all eighteen publications, the most commonly identified limitations included the lack of reporting on allocation concealment (n 16), the lack of reporting on the method of randomisation and thus the ‘appropriateness’ of the randomisation method, which also is a quality factor, could not be determined (n 13), as well as the lack of reporting of an intent-to-treat analysis (n 13).
Table 1. Key study characteristics of included studies (n 18 publications and 27 strata)

| References | Study design | Study duration | Study population (final sample size) | Age (years) | BMI (kg/m²) | Control | Almond intervention | Provision of control foods/diet |
|------------|--------------|----------------|-------------------------------------|-------------|-------------|---------|---------------------|--------------------------------|
| Abazarfard et al.⁹ | R, C, P | 12 weeks | 100 F; generally healthy; non-medicated | 42.7 ± 7.1* | 29.6 ± 1.5* | No nuts (n 50) | 50 g/d almonds (raw) as two snacks (about 25 g/snack) (n 50) | Hypoenergetic diet prescribed; foods were self-selected from a provided list |
| Berryman et al.¹¹ | R, C, X | 6 weeks (2 weeks WO) | 48 (22 M, 26 F); generally healthy; non-medicated | 49.9 ± 9.4 | 26.2 ± 2.8 | 106 g/d banana muffin with 2.7 g/d butter | 42.5 g/d (1.5 oz) whole almonds (unsalted, unroasted) | Meals prepared by a metabolic kitchen |
| Cohen & Johnston²⁴ | R, C, P | 12 weeks | 13 (7 M, 6 F); T2DM; medicated† | 66 ± 8.4* | 34.8 ± 8.0* | Two cheese sticks, 5 d/week (n 7) | 50 to 75 g/d almonds (raw, shelled, Spanish Marcona variety) || | Mediterranean-type diet prescribed; foods were self-selected || |
| Damasceno et al.¹⁹ | R, C, X, SB§ | 4 weeks (no WO) | 18 (9 M, 9 F); hypercholesterolaemic; non-medicated | 56 ± 13* | 25.7 ± 2.3* | 35 to 50 g/d olive oil | 56 g/d almonds (n 47)** | Low-energy diet prescribed; foods were self-selected || |
| Foster et al.¹⁴ | R, C, P | 18 months | 27 (15 M, 12 F); generally healthy; non-medicated | 46.8 ± 12.5* | 34.0 ± 3.6* | No nuts or peanut butter (n 45) | 37 ± 2 g/d whole almonds (raw, unblanched) with 75 ± 3 g/d muffin 73 ± 3 g/d whole almonds (raw, unblanched) | Self-selected low-fat therapeutic diet (selected following dietary instruction) |
| Jenkins et al. stratum 1²⁰ | R, C, X | 4 weeks (≥2 weeks WO) | 27 (15 M, 12 F); hyperlipidaemic; non-medicated†† | 64 ± 9 | 25.7 ± 3 | 147 ± 6 g muffin | Meals provided by army unit canteen |
| Jenkins et al. stratum 2²⁰ | R, C, P | 4 weeks | 30 M; generally healthy, habitual smokers; part of an army unit; medication status NR | 22.3 ± 1.8* | NR | No almonds (n 10) | 84 g/d (3 oz) almond powder (n 10) |
| Jia et al. stratum 1¹⁵ | R, C, P | 6 weeks | 47 F; healthy noncholesterolaemic; non-medicated‡‡ | 46.6 ± 9.4* | 25.7 ± 3.8* | No nuts or chocolate (n 12) | 168 g/d (6 oz) almond powder (n 10) | Dark chocolate and almonds provided; foods were otherwise self-selected |
| Kurlandsky & Stote stratum 1¹⁴ | R, C, P | 6 weeks | 47 F; healthy noncholesterolaemic; non-medicated‡‡ | 41.1 ± 10.2* | 25.5 ± 3.8* | 41 g/d dark chocolate (n 12) | 41 g/d dark chocolate and 60 g/d almonds (n 11) | Meals prepared by metabolic kitchen |
| Li et al.²⁵ | R, C, X | 4 weeks (2 weeks WO) | 20 (9 M, 11 F); T2DM; medicated§§ | 58 ± 2 | 26.0 ± 0.7 | No almonds | About 56 g/d whole almonds (roasted, unsalted, unblanched); 20 % of TDEI from almonds || |
| Lovejoy et al. stratum 1²⁹ | R, DB, X¶¶ | 4 weeks (2 weeks WO) | 30 (13 M, 17 F); T2DM; medicated*** | 53.8 ± 10.4 | 33.0 ± 1.0 | Olive oil or canola oil; fat comprised 25 % of TDEI, with 10 % from olive or canola oil | 57 to 113 g/d almonds (in meals and snacks); fat comprised 25 % of TDEI, with 10 % from almonds | Meals provided ||
| References                  | Study design | Study duration | Study population (final sample size) | Age (years) | BMI (kg/m²) | Control                                                                 | Almond intervention                                                                 | Provision of control foods/diet                                                                 |
|----------------------------|--------------|----------------|-------------------------------------|-------------|-------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Lovejoy et al. stratum 2   | R, C, P      | 4 weeks        | 26 (24 M, 24 F); medicated (on stable statin therapy‡‡‡) | 59.6 ± 11.1* | 29.2 ± 4.3* | Olive oil or canola oil; fat comprised 37 % of TDEI, with 10 % from olive or canola oil | 57 to 113 g/d almonds (in meals and snacks); fat comprised 37 % of TDEI, with 10 % from almonds | Diet counselling provided§§§                                                                 |
| Ruisinger et al.           | R, C, P      | 4 weeks        | 48 (24 M, 24 F); medicated (on stable statin therapy‡‡‡) | NR (20 to 60) | NR          | NCEP ATP III diet counselling (n 26)                                    | NCEP ATP III diet counselling and 100 g/d whole almonds (raw, unsalted) (n 22)       | Meals prepared by a metabolic kitchen****                                               |
| Sabaté et al. stratum 1    | R, C, X      | 4 weeks        | 25 (14 M, 11 F); generally healthy or mildly hypercholesterolaemic; non-medicated | NR (20 to 60) | NR          | No almonds                                                              | About 34 g almonds/2000 kcal (in meals and snacks); 10 % of TDEI from almonds       |                                                                                              |
| Sabaté et al. stratum 2    | R, C, P      | 4 weeks        | 45 (12 M, 33 F); generally healthy; non-medicated          | 53 ± 10†††† | NR          | 48 g/d olive oil, 113 g/d cottage cheese, and 21 g/d rye crackers (n 15) | 100 g/d whole or ground almonds (raw, unblanched) (n 18)                            |                                                                                              |
| Spiller et al. stratum 1   | R, C, P      | 4 weeks        | 21 (9 M, 12 F); T2DM; medicated§§§                          | 56.2 ± 7.5* | 35.3 ± 8.3* | No almonds                                                              | 43 g (1.5 oz) whole almonds, five to seven times/week (n 10)                         | Foods were self-selected                                                                 |
| Spiller et al. stratum 2   | R, C, P      | 4 weeks        | 30 (17 M, 13 F); hypercholesterolaemic; non-medicated       | 56 ± 6.1    | 24.1 ± 4.5  | No nuts, nut butter or margarines, or nut oils                           | 25 g/d almond powder                                                               | Foods were self-selected from a provided list                                             |
| Spiller et al. stratum 3   | R, C, P      | 4 weeks        | 137 (48 M, 89 F); at risk of T2DM; non-medicated§§§§         | 30.8 ± 10.6* | 27.6 ± 4.6* | No nuts or seeds (n 27)                                                  | 43 g/d almonds with breakfast (n 28)                                                 | Foods were self-selected                                                                 |
| Spiller et al. stratum 4   | R, C, P      | 4 weeks        | 28.2 ± 10.2*                                                | 27.9 ± 4.7* | SR          | 43 g/d almonds with lunch (n 26)                                       | 43 g/d almonds as afternoon snack (2 h after lunch and 2 h before dinner) (n 28)     |                                                                                              |
| Tan & Mattes stratum 1     | R, C, P      | 4 weeks        | 28.9 ± 10.8*                                                | 27.6 ± 4.8* | SR          | 43 g/d almonds as afternoon snack (2 h after lunch and 2 h before dinner) (n 28) |                                                                                         |                                                                                              |
| Tan & Mattes stratum 2     | R, C, P      | 4 weeks        | 29.0 ± 11.7*                                                | 28.0 ± 4.2* | SR          | 43 g/d almonds as afternoon snack (2 h after lunch and 2 h before dinner) (n 28) |                                                                                         |                                                                                              |
Low-energy liquid formula provided; complex CHO foods were self-selected from a provided list.

### R, C, P 24 weeks

- **52 (M and F): with a medical diagnosis that could benefit from weight reduction**
  - 55 ± 2.0* in CHO (n 28)
  - 38 ± 1.0* in low-energy liquid formula + complex CHO (n 28)

### R, C, P 16 weeks

- **54 (M and F); prediabetic††††‡‡‡‡; non-medicated††††**
  - 53.5 ± 10.1* in no tree nuts or peanuts (n 29)
  - 29.5 ± 5* in about 60 g/d almonds (raw or dry roasted)

About 60 g/d almonds were incorporated into the control diet to replace 20% of TDEI in the control diet; depending on the menus, almonds were either incorporated into entrées and desserts or consumed as a snack.

### Subjects

- **Subjects did not use lipid-lowering medications or dietary supplements. Subjects were allowed to be on stable regimens of oral contraceptives and HRT.**
- **Subjects did not receive insulin therapy; rather, all subjects were on stable oral hypoglycaemic therapy.**
- **All subjects were provided with whole-grain bread, brown rice, pasta, non-fat yogurt, rice cakes, dry beans, lentils, and couscous and were instructed to eat these foods a set number of times during each week. Subjects rounded out their daily times weekly. Up to four whole eggs were permitted/week, but only if the subject had been consuming eggs prior to the study. Foods not allowed included: commercial or homemade products containing fats other than the study fat, and products made with refined flour (e.g. snack foods, chips, crackers, cakes, pastries, pies, candy or ice cream).**
- **Usual coffee, tea, alcohol and soft drink consumption was permitted.**
- **Subjects on insulin therapy were excluded. Subjects taking prescription medications, including oral hypoglycaemic agents, statins or hypertensive medications were instructed to maintain consistent use throughout the study.**
- **Subjects were taking chronic statin therapy, defined as a consistent statin dose for at least 8 weeks before study entry with continuation of the same dose during the 4-week study period. Subjects who took lipid-lowering agents other than statins were excluded. Post-menopausal F who were not taking HRT or were on a consistent HRT dose were included. F of child-bearing potential using an effective form of contraception using an effective form of contraception were allowed to participate in the study.**
- **Subjects received NCEP ATP III diet counselling via telephone and instructions on how to compensate for the added energy from the almonds.**

### Background diet

Regarding background diets, on weekdays, the subjects were required to consume breakfast and dinner under supervision at the Pennington Biomedical Research Center’s dining facility; weekday lunches and snacks and all weekend meals were packaged for take-out.

### Subjects

- **Subjects were stratified according to the presence or absence of T2DM.**
- **Prediabetes was diagnosed according to the 2005 ADA diagnostic guidelines: fasting blood glucose between 100 and 125 mg/dl (5.56 and 6.94 mmol/l) or casual blood glucose ≥140–199 mg/dl (≥7.8–11.06 mmol/l).**

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Table 2. Summary of study design and duration, almond dose and baseline blood lipids

| References                  | Study design | Dose (g/d) | Control food/diet | Duration (weeks) | TC     | LDL-C  | HDL-C  | TAG     |
|-----------------------------|-------------|------------|-------------------|------------------|--------|--------|--------|---------|
| Abazarfard et al.(10)       | P           | X          | ≥45               | Pr               | ≥12    | BL*    | BL*    | BL*     |
| Berryman et al.(11)         | ✓           | ✓          | <45               | NPr              | <12    | EOT    | EOT    | EOT     |
| Cohen & Johnston(2-8)       | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Damasceno et al.(9)         | ✓           | ✓          | ≥45               | Pr               | ≥12    | BL*    | BL*    | BL*     |
| Foster et al.(18)           | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Jenkins et al. stratum 1(9) | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Jenkins et al. stratum 2(9) | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Kurlandsky & Stote stratum 1(14) | ✓       | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Kurlandsky & Stote stratum 2(14) | ✓       | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Li et al.(23)               | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Lovejoy et al. stratum 1(20) | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Lovejoy et al. stratum 2(20) | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Ruisinger et al.(27)        | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Sabaté et al. stratum 1(19) | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Sabaté et al. stratum 2(19) | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Spiller et al. stratum 1(27) | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Spiller et al. stratum 2(27) | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Sweazea et al.(10)          | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Tamizifar et al.(21)        | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Tan & Mattes stratum 1(23)  | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Tan & Mattes stratum 2(23)  | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Tan & Mattes stratum 3(23)  | ✓           | ✓          | ≥45               | Pr               | ≥12    | O      | O      | O       |
| Tan & Mattes stratum 4(23)  | ✓           | ✓          | ≥45               | Pr               | ≥12    | O      | O      | O       |
| Wien et al.(29)             | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Wien et al.(29)             | ✓           | ✓          | ≥45               | Pr               | ≥12    | N.O.   | N.O.   | N.O.    |
| Total                       | 17          | 10         | 17                | 10               | 14     | 13     | 21     | 6       |

TC, total cholesterol; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; P, parallel; X, crossover; Pr, provided; NPr, not provided; BL, baseline; EOT, end of treatment; N.O., not optimal; O, optimal; –, not reported.

*Mean baseline TC, LDL-C, HDL-C and TAG were categorised as O or N.O., based on the targets established in the National Cholesterol Education Program Adult Treatment Panel III guidelines (i.e. optimal blood lipid levels were defined as: TC ≤ 5.17 mmol/l; LDL-C ≤ 2.59 mmol/l; HDL-C ≥ 1.03 mmol/l; TAG < 1.69 mmol/l).
† In the study by Spiller et al. strata 1 and 2(27), HDL-C and TAG levels were assessed at BL and at EOT; however, values were presented only in figure form, with no measures of variability. The results related to HDL-C and TAG could not be included in the meta-analyses.
whether TAG levels at baseline were or were not optimal could not be made. In the study by Spiller et al. strata 1 and 2\(^{(7)}\), TC, LDL-C, HDL-C and TAG were assessed at baseline and at the end of treatment; however, only the results for TC and LDL-C at the end of treatment were reported. Thus, the HDL-C and TAG results could not be included in the meta-analyses, and in order to include the results related to TC and LDL-C in the meta-analyses, the mean difference in the effect for TC and LDL-C had to be calculated by subtracting the end-of-treatment value in the control group from the changes from baseline in the almond group (as opposed to subtracting the changes from baseline in the control group from the changes from baseline in the almond group, which was done for all other parallel studies).

The effects of almonds on fasting TC levels were assessed in all twenty-seven strata. The daily almond intake was 45 g or greater in 63 % of the strata, the design was crossover in 37 % of the strata, the baseline fasting TC level was not optimal in 52 % of the strata, a control food/diet was provided in 52 % of the strata, and the study duration was <12 weeks in 78 % of the strata (Table 3). As can be seen in Table 3 and Fig. 2, the reduction in TC was statistically significant when data from all twenty-seven strata were pooled (−0.153 mmol/l; 95 % CI −0.235, −0.070 mmol/l; \( P < 0.001 \)). As there was no publication bias identified, no adjustment to these values was made. In all of the subgroup analyses, the pooled effect sizes for TC were negative. Statistical significance was observed when pooling those strata in which the almond dose was ≥45 g/\( d \), the baseline TC level was not optimal, the study design was either parallel or crossover, the control food/diet either was or was not provided, and the duration of the almond intervention period was <12 weeks (Table 3).

The effects of almonds on fasting LDL-C were assessed in twenty-five strata. The daily almond intake was 45 g or greater in 60 % of the strata, the design was crossover in 40 % of the strata, the baseline fasting LDL-C level was not optimal in 80 % of the strata, a control food/diet was provided in 48 % of the strata, and the study duration was <12 weeks in 76 % of the strata (Table 3). As can be seen in Table 3 and Fig. 3, the reduction in LDL-C was statistically significant when data from all twenty-five strata were pooled (−0.124 mmol/l; 95 % CI −0.196, −0.051 mmol/l; \( P = 0.001 \)). As there was no publication bias identified, no adjustment to these values was made. In all of the subgroup analyses, the pooled effect sizes for LDL-C were negative. Statistical significance was observed when pooling those strata in which the almond dose was ≥45 g/\( d \), the baseline LDL-C level was not optimal, the study design was crossover, a control food/diet was provided, and the study duration was <12 weeks (Table 3). It should be noted that when the control-adjusted changes in LDL-C for the thirteen strata in which the control food/diet was not provided were pooled, the reduction in LDL-C approached statistical significance (\( P = 0.068 \)).

Almond consumption was not associated with any significant effect on fasting HDL-C, either in the overall analysis in which all twenty-two strata were pooled or in any of the subgroup analyses (Table 3 and Fig. 4).

The effects of almonds on fasting TAG were assessed in twenty-five strata. The almond intake was 45 g or greater in 60 % of the strata, the design was crossover in 40 % of the strata, the baseline fasting TAG level was not optimal in 30 % of the strata, a control food/diet was provided in 48 % of the strata, and the study duration was <12 weeks in 76 % of the strata (Table 3). As can be seen in Table 3 and Fig. 5, the reduction in TAG was statistically significant when data from all twenty-five strata were pooled (−0.067 mmol/l; 95 % CI −0.132, −0.002 mmol/l; \( P = 0.042 \)). As there was no publication bias identified, no adjustment to these values was made. In all of the subgroup analyses, the pooled effect sizes for TAG were negative but not statistically significant, except for when the fifteen strata in which the study design was parallel were pooled, and the resultant pooled effect was a statistically significant reduction in TAG (−0.111 mmol/l; 95 % CI −0.204, −0.017; \( P = 0.020 \)). Through additional sensitivity analyses, it was determined that this effect was dependent on the inclusion of the parallel study by Abazari Fach et al.\(^{(7)}\), which included 100 females and was a relatively larger study.

With regards to the ratio of TC:HDL-C, when data from all nine strata were pooled, the reduction in the ratio was statistically significant (see Table 3 and Fig. 6). However, publication bias was detected. Using trim and fill, two studies were found to be missing to the right of the pooled effect size, and with these studies imputed, the pooled effect, though negative (i.e. favourable), was smaller and no longer statistically significant (Table 3). Results for the subgroup analyses were in the same direction of effect (i.e. the pooled effect was negative), with variable statistical significance. With regards to the ratio of LDL-C:HDL-C, when data from all ten strata were pooled, the reduction in the ratio was not significant (−0.089; 95 % CI −0.209, 0.031; \( P = 0.145 \)) (see Table 3 and Fig. 7). As for the ratio of TC:HDLC, publication bias was detected, and using trim and fill, two studies were found to be missing to the right of the pooled effect size for LDL-C:HDL-C. With these studies imputed, the pooled effect, though negative (i.e. favourable), was smaller and remained non-statistically significant (Table 3). Results for the subgroup analyses were in the same direction of effect (i.e. the pooled effect was negative), with variable statistical significance.

**Discussion**

In a meta-analysis that included five randomised control trials (and nine strata), Phung et al.\(^{(7)}\) reported that almonds significantly reduce TC and have a strong trend towards reducing LDL-C (\( P = 0.05 \)). Although Phung et al.\(^{(7)}\) also reported a near-significant reduction in HDL-C (\( P = 0.08 \)) and no effect on TAG, in our analyses, which are based on a total of eighteen publications and twenty-seven strata, the intake of almonds was associated with significant reductions in TC, LDL-C and TAG, and no effects on HDL-C.

In a meta-analysis and dose–response of sixty-one controlled intervention trials, which ranged in duration from 3 to 26 weeks, the consumption of nuts was associated with...
Effects of almonds on blood lipid levels: results of meta-analyses of randomised controlled trials*

Table 3. Effects of almonds on blood lipid levels: results of meta-analyses of randomised controlled trials

| Study design | Baseline lipid level | Almond dose (g/d) | TAG (mmol/l) | TC:HDL-C | LDL-C (mmol/l) | HDL-C (mmol/l) | TC (mmol/l) |
|-------------|----------------------|------------------|--------------|----------|----------------|----------------|-------------|
| Crossover   | <45                  | 27               | 0.071 (0.018, 0.100) | 0.017 (0.004, 0.030) | 0.018 (0.004, 0.030) | 0.002 (0.001, 0.003) | 0.106 (0.033, 0.165) |
| Parallel    | <45                  | 22               | 0.071 (0.018, 0.100) | 0.017 (0.004, 0.030) | 0.018 (0.004, 0.030) | 0.002 (0.001, 0.003) | 0.106 (0.033, 0.165) |
| Crossover   | <45                  | 25               | 0.071 (0.018, 0.100) | 0.017 (0.004, 0.030) | 0.018 (0.004, 0.030) | 0.002 (0.001, 0.003) | 0.106 (0.033, 0.165) |
| Parallel    | <45                  | 25               | 0.071 (0.018, 0.100) | 0.017 (0.004, 0.030) | 0.018 (0.004, 0.030) | 0.002 (0.001, 0.003) | 0.106 (0.033, 0.165) |
| Crossover   | <45                  | 22               | 0.071 (0.018, 0.100) | 0.017 (0.004, 0.030) | 0.018 (0.004, 0.030) | 0.002 (0.001, 0.003) | 0.106 (0.033, 0.165) |
| Parallel    | <45                  | 25               | 0.071 (0.018, 0.100) | 0.017 (0.004, 0.030) | 0.018 (0.004, 0.030) | 0.002 (0.001, 0.003) | 0.106 (0.033, 0.165) |

*An assessment of publication bias was conducted for each lipid parameter, but only for the meta-analysis that included all strata. Publication bias was not identified for TC, LDL-C, HDL-C or TAG. For the ratio of TC:HDL-C, two studies were found to be missing to the right of the pooled estimate, and the pooled estimate was <0.105 (95% CI: 0.062, 0.148). For the ratio of LDL-C:HDL-C, two studies were found to be missing to the right of the pooled estimate, and the pooled estimate was <0.132 (95% CI: 0.089, 0.175).
significant reductions in TC, LDL-C, apoB and TAG, with greater effects observed with a nut intake of 60 g/d and in individuals with T2DM(29). In contrast, in a Cochrane review, Martin et al.(30) reported that the intake of nuts had no effects on LDL-C or HDL-C (for TC and TAG, substantial heterogeneity precluded the pooling of results). The Cochrane assessment was based only on three publications (and four strata): Tey et al.(31) (who provided 42 g of hazelnuts to generally healthy male and female adults for 12 weeks); Abazfarad et al.(30) (who provided 50 g of almonds to overweight and obese premenopausal women for 3 months); and Tey et al.(32) (who provided 30 or 60 g of hazelnuts to overweight and obese male and female adults for 12 weeks). The main objective of the Cochrane review was to assess the effects of nut consumption on the primary prevention of CVD. In none of the studies was the incidence of heart disease assessed; thus, the effects of nut consumption on surrogate measures of CVD risk were examined. With such few studies,
and with three of the four strata conducted in generally healthy subjects, it is no surprise that effects on blood lipid levels could not be identified.

Based on our systematic evidence-based review and meta-analyses, which included a total of eighteen publications and twenty-seven strata, the intake of almonds was associated with significant reductions in TC, LDL-C and TAG, and no effects on HDL-C. In all of the included studies, almonds or diets enriched with almonds were provided to the subjects; however, the control was variable across the studies. In thirteen of the twenty-seven strata, a control food or diet was not administered to the subjects and the subjects were instructed not to consume nuts. In fourteen of the twenty-seven strata, the subjects were provided with a control food or a control diet. It seems that almonds effectively improve TC and LDL-C, whether the comparison is made with the consumption of no almonds or with a control food or diet that, at the very least, was isocaloric to the almond intervention. Based on the other subgroup analyses, it seems that the efficacy of almonds in improving TC and LDL-C is greatest with a daily almond intake of 45 g or more and in individuals whose TC and LDL-C levels at baseline are elevated (i.e. not optimal). Although pooling the results of the crossover studies (but not the parallel studies) resulted in a significant reduction in LDL-C, the results should be interpreted with caution, given that the crossover strata were comprised...
predominantly of subjects whose baseline LDL-C levels were not optimal, while the parallel strata were comprised predominantly of subjects whose baseline LDL-C levels were optimal. Likewise, although pooling the results of the studies with a duration <12 weeks (but not the studies with a duration ≥12 weeks) resulted in significant reductions in both TC and LDL-C, the results should be interpreted with caution, given that there were only six strata with a duration ≥12 weeks, and in three of these six strata, the intake of almonds was <45 g/d and/or the subjects had optimal levels of TC and/or LDL-C at baseline(10,16,24). Of the three parallel strata that were 12 weeks or longer in duration and in which the almond intake was ≥45 g/d and the baseline lipid levels were not optimal, there were significant or near-significant reductions in both TC and LDL-C in two of the strata(9,23).

There is preliminary evidence that the consumption of almonds also leads to favourable changes in the ratio of TC:HDL-C; however, this lipid parameter was assessed only in nine strata, and the improvement was no longer statistically significant once an adjustment for publication bias was made. Preliminary evidence that the consumption of almonds leads to favourable changes in the ratio of TC:HDL-C is consistent with our findings of significant reductions in TC, with no effects on HDL-C. LDL-C as well as the ratio of TC:HDL-C are recognised as surrogate measures of CHD risk. Thus, it is plausible that by improving the blood lipid profile, the consumption of almonds would also be associated with significant reductions in the risk of CHD. While an intervention study on the effects of almonds on the risk of CHD has yet to be conducted, there is evidence from both prospective observational studies and a randomised controlled trial that the consumption of nuts, in general, is associated with significant reductions in the incidence of heart disease (discussed in the following paragraph).

In a meta-analysis of thirteen prospective studies (involving a total of 347 477 individuals and 6127 cases of coronary artery disease (CAD)), the relative risk (RR) of CAD was significantly reduced with the highest 𝑛. the lowest consumption of nuts (RR 0.660; 95 % CI 0.581, 0.748); moreover, the protective effect of nuts against the development of CAD was found to be dose-dependent, such that risk decreased by 5 % for every additional serving of nuts consumed per week(33). In the PREDIMED (PREvención con DIeta MEDiterránea) study, which is a large, multi-centre primary prevention trial of the effects of three diets on CVD risk, the consumption of a Mediterranean diet supplemented with either extra-virgin olive oil or nuts resulted in significant reductions in CVD cases (including cases of myocardial infarction, stroke, or CVD death) relative to a control group instructed to consume a diet low in fat(34). In a recent cross-sectional study involving 3 312 403 Americans undergoing screening for peripheral arterial disease, those who consumed nuts every day were 21 % less likely to have peripheral arterial disease relative to those who consumed nuts less than once per month; this statistically significant.
significant finding was evident even after adjusting for several important variables, such as age, sex, smoking status, obesity, family history of CVD, diet and the presence of diet-related diseases such as diabetes\(^{(35)}\).

The mechanism by which the consumption of nuts leads to favourable alternations in blood lipid levels is not fully understood. Nuts are nutrient dense, have a favourable fatty acid profile, and contain other constituents such as sterols and flavonoids that, collectively, may be important in the mechanism of almonds in improving blood lipid levels and CHD risk. In addition, it is possible that the favourable changes in blood lipid levels with the consumption of almonds are related, at least in part, to concomitant improvements in body weight and body composition. In several of the studies that were included in our meta-analysis, there were significant reductions in body weight with the consumption of almonds relative to the control\(^{(11,20,28)}\). The study by Berryman et al.\(^{(11)}\) is of particular interest, given that the subjects were provided with all of their foods during both the almond and control intervention periods, and the diets were rigorously controlled. There were statistically significant improvements in body weight, waist circumference and body composition (including abdominal fat mass) with the 6-week consumption of the almond diet relative to the control diet. Recently, it was demonstrated that the energy value of almonds calculated using the Atwater factors is 32 % greater than the actual energy that is metabolisable from almonds\(^{(36)}\). Similar observations have also been made for pistachios and walnuts\(^{(37,38)}\). This could explain the reductions in body weight that have been observed in some of the studies with the consumption of almonds. If not all of the ‘calculated’ energy in almonds is actually metabolisable, then in highly controlled experimental studies where the diets are prepared and provided to the study participants (such as in the study by Berryman et al.\(^{(11)}\)), the diets may not have been truly isocaloric.

The consumption of nuts is encouraged in several ‘heart-healthy’ diets. Nuts are important constituents of the portfolio diet, which also consists of plant sterols, viscous fibres and soya protein\(^{(39)}\). Likewise, nuts are part of the Mediterranean diet, which consists also of fruits and vegetables, legumes, whole-grain cereals, olive oil, fish and seafood, herbs and spices, and moderate amounts of meat, dairy products and wine\(^{(40)}\). Nuts are constituents of the Palaeolithic diet, which also includes lean meat, fish, fruit, leafy and cruciferous vegetables, root vegetables and eggs\(^{(41)}\). The consumption of nuts, such as almonds, as part of a healthy diet should be encouraged in order to help in the maintenance of normal blood lipid levels and to reduce the risk of heart disease.

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