



FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

Systematic Review of the Evidence for a Relationship between Pectins and Blood Cholesterol Concentrations

Prepared by: Food Standards Australia New Zealand

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Executive Summary

<i>Does pectin intake affect blood total cholesterol concentration?</i>	
Food-health relationship	Increased pectin consumption reduces blood total cholesterol concentrations
GRADE rating	Total cholesterol: Moderate ⊕⊕⊕
Component	Notes
Body of evidence	Most studies which were included in a published 1999 meta-analysis and a 1987 review of the relationship between pectin and blood total cholesterol could not be included in the body of evidence because they included foods with a mixture of dietary fibres and/or undefined pectin content. Seven randomised control trials (RCTs) met the inclusion criteria and were used to examine the relationship.
Consistency	There is a high degree of consistency between the RCTs, with most studies supporting the relationship and two finding no relationship between pectin in food and blood total cholesterol.
Causality	Although RCTs are a strong design for showing causality, this has not been established, as the number and sample size of the high quality studies is low. Three of four high quality studies showed a reduction in blood total cholesterol but one study showed a small, non-significant increase in blood total cholesterol.
Plausibility	There is a plausible mechanism for lowering blood total cholesterol via soluble dietary fibre, due to physical inhibition of bile acid re-uptake.
Generalisability	The studies came from the UK, USA and continental Europe so they should be generally applicable to New Zealand and Australia. No studies in non-Caucasian populations were identified. The only study conducted in people with normal cholesterol concentrations was rated as low quality.

FSANZ has conducted a systematic review on pectin consumption and blood total cholesterol concentrations. In doing this review, FSANZ has followed the requirements of the *Application Handbook* and of Schedule 6 of Standard 1.2.7 – Nutrition, Health and Related claims, for the required elements of a systematic review.

Seven RCTs met the selection criteria and tested 9-36g pectin/day. Three of these trials were at high risk of bias, and four studies were of high quality, with a low risk of bias. Of these high quality studies, three found a statistically significant association between pectin consumption and reduced blood total cholesterol, whereas one study found a small, non-significant increase in blood total cholesterol. Only one study (a low quality study) was conducted in people with normal cholesterol concentrations.

In spite of a plausible mechanism of action the degree of certainty in the relationship between pectin consumption and reduced blood total cholesterol is considered to be only 'Moderate'. Furthermore, there is very little reliable evidence that pectins lower blood total cholesterol in people with normal cholesterol concentrations (<5.5mmol/L). Consequently, FSANZ has rated the relationship between pectin consumption and blood total cholesterol as 'Moderate'.

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1 Introduction

In 2012, the European Union authorised a claim that 'pectins contribute to the maintenance of normal blood cholesterol levels' under Article 13(1) which permits function claims (European Commission regulation (EU) No 432/2012 of 16/05/2012). FSANZ notes that the evidence assessed by the European Food Safety Authority (EFSA), on which this claim was based, referred to a lowering of blood cholesterol concentrations (EFSA, 2010). The EFSA conclusions were based on the examination of one review and one meta-analysis (Reiser, 1987; Brown et al. 1999) but these were not formally updated. FSANZ notes that the Brown meta-analysis included studies with foods containing a range of fibres and undefined pectin content.

FSANZ is considering whether a relationship between pectin intake and blood total cholesterol can be incorporated into Schedule 2 of Standard 1.2.7.

The purpose of this paper is to systematically review the evidence for the relationship between pectin intake and blood total cholesterol concentrations.

1.1 Property of food

Dietary carbohydrates can be classified into two distinct groups depending upon their digestibility in the gastrointestinal tract – those that can be metabolised and ones which are fermented by micro-organisms that are predominant in the colon. The latter are generally referred to as dietary fibres of which pectin is an example. Since only monosaccharides (ie. simple sugars) are readily absorbed in the upper part of the gastrointestinal tract the chemical configuration and intra-molecular linkage of the D-saccharides are important determinants for release of monosaccharides (sugars). Since most mammalian enzymes can only cleave D-saccharides linked by α 1:4 glycosidic bonds, all other saccharides having different glycosidic linkages (with the exception of lactose) will pass undigested into the colon. Resistant starch is also an exception because, although the linkages are α 1:4 glycosidic, most passes undigested into the colon.

A second group of dietary carbohydrates contains the branched carbohydrates and are frequently components of plant cell walls. This group of fermentable carbohydrates can be further subdivided into the two groups based on their water solubility. The more soluble ones, such as pectin, beta-glucans or inulin-type fructans form viscous gels in water and are relatively easily fermented to short chain fatty acids by microflora of the large intestine. The second group, which includes lignin, cellulose and some hemicelluloses, are mostly insoluble. These latter carbohydrates do not form gels due to their water insolubility and so extensive fermentation by microbiota in the large intestine is also limited.

Both soluble and insoluble forms of fermentable carbohydrates constitute dietary fibre. FSANZ defines dietary fibre in Standard 1.2.8 – Nutrition Information Requirements of the *Australia New Zealand Food Standards Code* (Code) as follows:

dietary fibre means that fraction of the edible part of plants or their extracts, or synthetic analogues that –

- (a) are resistant to the digestion and absorption in the small intestine, usually with complete or partial fermentation in the large intestine; and*
- (b) promote one or more of the following beneficial physiological effects –*
 - (i) laxation;*
 - (ii) reduction in blood cholesterol;*

*(iii) modulation of blood glucose;
and includes polysaccharides, oligosaccharides (degree of polymerisation > 2) and lignins.*

Pectins are rich in galacturonic acid, although they contain other monosaccharides as well. In nature, around 80% of carboxyl groups of galacturonic acid are esterified with methanol. This proportion decreases during extraction, leading to high- versus low-ester pectins.

Pectin consumption in 'typical' Western countries is estimated to be around 5 g per day (Srivastava and May 2011). They are mostly ingested from fruits, where they can be found in significant amounts in pome fruits, plums, gooseberries, citrus fruits (especially the peel) and in some vegetables such as carrots.

Pectin is permitted to be added as a food additive to processed foods in Australia and New Zealand at good manufacturing practice levels (Standard 1.3.1 – Food Additives¹, of the Code).

1.2 Health effect

The health effect examined by FSANZ was that consumption of pectin 'reduces blood cholesterol. Reductions in total and low density lipoprotein (LDL) cholesterol are considered to be a beneficial health effect due to elevated levels of these blood lipids being risk factors for coronary heart disease (CHD). In contrast, although high density lipoprotein (HDL) cholesterol concentrations are inversely related to CHD, their predictive power for CHD incidence is less certain.

Total cholesterol can be measured in serum or plasma. Following saponification to release free cholesterol from cholesterol esters, cholesterol is then extracted and measured using a colourimetric reaction. LDL-cholesterol can be measured directly following separation by ultracentrifugation, or, more commonly, is calculated from direct measures of total, HDL and triglyceride levels using the Friedewald equation².

Hypercholesterolaemia is described in Australia as being total serum cholesterol concentrations ≥ 5.5 mmol/L³

1.3 Proposed relationship

The food-health relationship being assessed in this report is that increased pectin consumption reduces blood total cholesterol concentrations.

2 Evaluation of evidence

2.1 Methods

2.1.1 Search strategy

A search was conducted in EMBASE on December 5th, 2013 and repeated in PubMed and the Cochrane library the following day. There were no restrictions in dates. Detailed search

¹ Standard 1.3.1 – Food Additives is available at <http://www.foodstandards.gov.au/code/Pages/default.aspx>

² Friedewald equation calculates LDL cholesterol using the following formula:

LDL = total cholesterol – HDL cholesterol – (triglyceride / 2.2) where all concentration are in mmol/L

³ This cut-off point is used in the Australian Health Survey and by the Therapeutic Goods Administration <https://www.tga.gov.au/book/part-b-further-technical-guidance>

strategies are presented in Appendix 1. Two papers were also identified by searching the reference lists of other papers.

2.1.2 Inclusion and exclusion criteria

To be included in the systematic review the trial must have been randomised and include an appropriate control group. Study participants could be adults or children (>2 years of age), and could include individuals with chronic non-communicable diseases such as diabetes, hyperlipidaemia or hypertension.

The pectin intervention could be given in various ways as long as an appropriate control was available. For example, pectin-rich food versus equivalent food without pectin, pectin made into food (e.g. pectin powder dissolved in marmalade spread on bread versus the marmalade without additional pectin) or packets of pectin powder consumed with food (e.g. sprinkled on breakfast cereal) versus no powder, pectin supplements given as capsules versus placebo capsules. Consequently, not all the studies were blind.

Studies using pectin with other fibres (referred to as mixed fibre studies) were excluded. This criterion also excludes studies which fed a single food (e.g. guavas) because these contain a mixture of fibres and so any effects could not be attributed to pectin alone.

Outcome measures of at least total cholesterol were required, but studies measuring other outcomes were acceptable as long as they also measured total cholesterol.

The minimum duration of trials was 2 weeks which is considered sufficient for changes in blood lipid outcomes to stabilise (Brussaard et al. 1982; Mensink and Katan 1987). Parallel, cross-over and Latin-square designs were acceptable. Sequential designs were excluded.

An additional inclusion criterion was the reporting of background dietary intakes so that equality of fatty acid and fibre intakes could be assessed because cholesterol concentrations are affected by many factors. This criterion was only implemented for parallel studies and unblinded cross-over studies. Because the same subjects are used in both arms in a cross-over design, it was assumed that background diet would remain constant if the study subjects were blind.

In studies which reported cholesterol concentrations for multiple time points, the baseline and end of intervention (or control) arm data were extracted.

When data were missing from papers, the authors were contacted. Additional data supplied by authors are annotated in this report where used.

Table 1 *PICOTS criteria for study selection*

Population	Non-acutely ill adults or children
Intervention	Increased consumption of pectin in foods or as a supplement
Comparator	Placebo or same foods without pectin
Outcome	Total cholesterol concentrations
Time	At least 2 weeks duration of the intervention and comparison intakes
Study design	Randomised controlled trial

2.1.3 Unpublished material

The WHO International Clinical Trials Registry Platform was also searched to identify potentially unreported or impending clinical trials on pectin and cholesterol.

2.1.4 Study selection, data extraction and quality assessment

Records identified during the search process were imported into EPPI-Reviewer 4 (<http://eppi.ioe.ac.uk/cms/er4>). Following removal of duplicates, records were screened on title and abstract. Candidate full-text articles were retrieved and assessed against the inclusion/exclusion criteria. Screening was conducted by one investigator.

Total cholesterol data were extracted by one investigator and cross-checked by a second investigator, as was background dietary fibre intake. Trials were assessed for risk of bias according to the Cochrane Handbook (Higgins and Green 2011), and were collated using Review Manager version 5.2 which was developed by The Nordic Cochrane Centre. All studies were assessed by a second investigator and risk of bias assessments were found to be concordant between investigators.

2.1.5 Statistical analyses

Following data extraction, changes in blood cholesterol concentrations were calculated if final results were not reported by study authors. For cross-over studies the difference in blood cholesterol concentrations were calculated as:

$$\text{Difference} = \text{Cholesterol}_{(\text{end of intervention})} - \text{Cholesterol}_{(\text{end of control})}$$

and its standard error of the mean (SEM) as:

$$\text{SEM} = \sqrt{[(\text{SEM}_{(\text{end of intervention})})^2 + \text{SEM}_{(\text{end of control})}^2] - 2r(\text{SEM}_{(\text{end of intervention})})(\text{SEM}_{(\text{end of control})})}$$

For parallel studies reporting the change in each group, the difference between the groups was calculated as:

$$\text{Difference} = (\text{Cholesterol}_{(\text{change in intervention gp})} - \text{Cholesterol}_{(\text{change in control gp})})$$

and its standard error as:

$$\text{SEM} = \sqrt{[(\text{SEM}_{(\text{change in intervention gp})})^2 + \text{SEM}_{(\text{change in control gp})}^2]}$$

For parallel studies, which did not report change values and their standard error, the difference in blood cholesterol between groups was calculated as:

$$\text{Difference} = (\text{Cholesterol}_{(\text{end, intervention})} - \text{Cholesterol}_{(\text{baseline, intervention})}) - (\text{Cholesterol}_{(\text{end, control})} - \text{Cholesterol}_{(\text{baseline, control})})$$

and its standard error as:

$$\text{SEM} = \sqrt{(\text{SEM1}^2 + \text{SEM2}^2)}, \text{ where}$$

$$\text{SEM1} = \sqrt{[(\text{SEM}_{(\text{end, intervention})}^2 + \text{SEM}_{(\text{baseline, intervention})}^2) - 2r((\text{SEM}_{(\text{end, intervention})})(\text{SEM}_{(\text{baseline, intervention})}))]}$$

$$\text{SEM2} = \sqrt{[(\text{SEM}_{(\text{end, control})}^2 + \text{SEM}_{(\text{baseline, control})}^2) - 2r((\text{SEM}_{(\text{end, control})})(\text{SEM}_{(\text{baseline, control})}))]}$$

$r = 0.8$ was used as the correlation coefficient between repeated measures of blood cholesterol (Demonty et al. 2009, FSANZ 2011).

Meta-analysis was performed using a random effects model and generic inverse variance method to allow combination of the varied data reporting methods, and to ensure cross-over studies were not given less weight compared to parallel studies. The meta-analysis was performed using Review Manager (RevMan) version 5.3, the systematic review software developed by The Cochrane Collaboration (The Nordic Cochrane Centre 2014). RevMan v5.3 was also used to calculate standard error only where variance data were presented as confidence intervals or as a p-value.

I^2 was used to assess heterogeneity among the strata. It describes the 'percentage of total variation across studies that is due to heterogeneity rather than chance' and 0%, 25%, 50% and 75% could be interpreted as indicating no, low, medium and high heterogeneity respectively (Higgins et al. 2003).

2.1.6 Subgroup analyses

The following subgroup analyses were identified *a priori* to explore differences in effect sizes, but were not carried out as the number of included studies was too small:

- pectin type (e.g. high- vs low-methoxyl pectins)
- use or not of concomitant lipid-lowering medication among trials of hypercholesterolaemic subjects
- amount of pectin
- parallel or cross-over study design
- baseline dietary fibre intake
- gender
- adults compared to children
- diabetes status
- funding source (industry/not industry)
- high compared with low quality studies.

The following subgroup analysis was carried out:

- populations with normal blood cholesterol (mean group cholesterol <5.5 mmol/L) vs hypercholesterolaemic subjects (mean group cholesterol ≥5.5 mmol/L).

2.2 Results

2.2.1 Search results

The screening of articles retrieved from the search strategies is detailed in Figure 1. Studies excluded after full text examination are listed in Appendix 2.

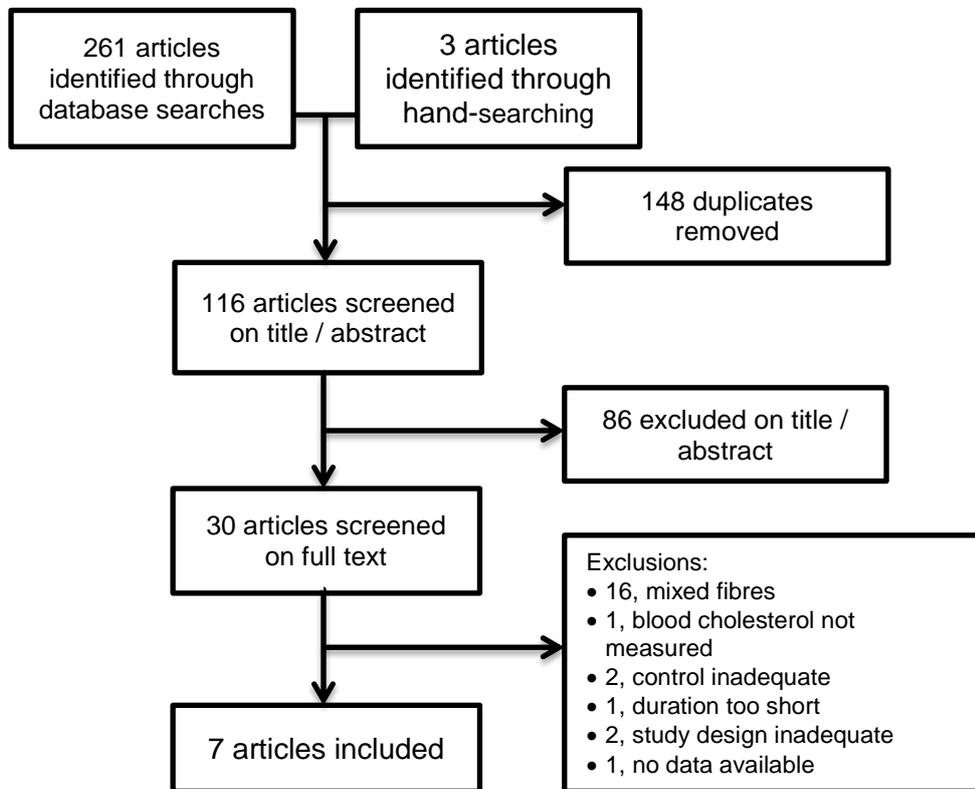


Figure 1 PRISMA diagram for selection of studies

2.2.2 Included studies

After completing the detailed full-text review, seven articles were included in the final analysis. None of the articles describe the results of more than one study and thus seven studies were considered in the review. The details of the studies are included in

Table 2, with the assessment of bias in Figure 2. Of the seven studies, four were published prior to 1990. Two of the older studies state that they were conducted in healthy or normo-cholesterolaemic subjects (Challen et al. 1983; Hillman et al. 1985), whereas the more recent studies state they were conducted in people with mild-moderate hypercholesterolaemia. However, the baseline data of the older studies show mean cholesterol concentrations in all but one case that would be regarded as treatable in modern times and are similar to those in the modern studies. Using the criteria given in Section 2.1.6, FSANZ regards all studies except Stasse-Wolthuis et al.(1980) as having been conducted in groups with at least mild hypercholesterolaemia.

The amount of pectin used ranged 4-fold across the studies, from 9 g to 36 g/day with six studies using amounts between 9-16 g/day. All studies reported data for total cholesterol

Table 2 Study details of the seven included studies

Reference	Brouns et al. 2012
Study design	Four-week, cross-over, double blind
Objectives	To examine the effect of degree of esterification and molecular weight on cholesterol-lowering properties of pectin
Sample size	30 enrolled, 29 completed; sample size calculation assumed a difference of 0.47 mmol/L LDL cholesterol
Participants	Healthy, mildly hyper-cholesterolaemic people around 58 years
Interventions	15g pectin per day in food products or identical placebo food products
Methods	Total cholesterol was measured using the CHOD-PAP method.
Confounders	Controlled by crossover design, as well as double blinding and use of placebos
Results	Total cholesterol: Control: baseline 6.5 ± 0.17 , end 6.63 ± 0.17 Pectin: baseline 6.45 ± 0.17 , end 6.18 ± 0.15 (Mean\pmSEM)
Difference	-0.45 ± 0.10 $p < 0.00001$ (p-value calculated in Review Manager)
Notes	Various kinds of pectin trialled. The apple pectin DE-70 was chosen as it is closest to the DE of pectin consumed in food. Actual pectin intake was 14g per day.
Adverse effects	Some flatulence observed. No other statistically significant differences in adverse effects noted.
Funding source	Cargill European R&D Centre (Vilvoorde, Belgium)

Reference	Cerda et al.1988
Study design	16 week, double-blind, crossover
Objectives	To study the effects of grapefruit pectin on hyper-cholesterolaemic people without changing diet or lifestyle
Sample size	27 analysed; no sample size calculations given
Participants	Healthy volunteers aged 27 - 69 with hypercholesterolemia
Interventions	15g high DE grapefruit pectin or placebo taken as 27 capsule per day over three meals
Methods	Total cholesterol was measured enzymatically
Confounders	Controlled by double blinding, crossover design and placebo
Results	Total cholesterol: baseline: 7.1 ± 0.28 ; control: 7.1 ± 0.3 ; pectin 6.6 ± 0.3 (Mean \pmSEM)
Difference	-0.5 ± 0.19 $p = 0.008$ (p-value calculated in Review Manager)
Notes	None
Adverse effects	No adverse effects were noted
Funding source	Florida Citrus Commission and NIH

Reference	Challen et al. 1983
Study design	Randomised, controlled, crossover trial (not blinded)
Objectives	To study the effects of pectin and wheat bran on platelet function and haemostasis in people.
Sample size	Six analysed; no sample size calculations given
Participants	Male volunteers aged 21-40 years, fit and healthy
Interventions	36g pectin as dry powder mixed with food throughout the day for three weeks. After three weeks the participants swapped to food without added pectin or vice versa. All foods were provided by the research lab. (Wheat bran tested in a separate arm.)
Methods	Method of cholesterol determination was not stated. Paired two-tailed <i>t</i> test used for statistical analysis
Confounders	Controlled by crossover design and provision of all foods during the trial.
Results	Total cholesterol: baseline: 5.67 ± 0.45 , end: control: 5.73 ± 0.36 , pectin: 5.18 ± 0.35 (Mean\pmSEM)

Difference	Total cholesterol: -0.55±0.22 p=0.01 (p-value calculated in Review Manager)
Notes	None
Adverse effects	No adverse effects were noted.
Funding source	None stated

Reference	Hillman et al. 1985
Study design	Randomised, controlled, crossover trial (not blinded)
Objectives	To study the effects of pectin, cellulose and lignin on serum cholesterol concentrations.
Sample size	10 analysed: no sample size calculations given
Participants	2 males and 8 females, mean age 30.9 ±7.9 years, healthy volunteers.
Interventions	12g pectin as dry powder mixed with food throughout the day for three weeks. After four weeks the participants swapped to food without added pectin. The participants consumed their normal diets during both periods.
Methods	Serum cholesterol was measured using an enzymatic colorimetric method. The results were compared using a Student's <i>t</i> test for paired data.
Confounders	Controlled by crossover design.
Results	Total cholesterol: (end of study) control: 5.8±0.35, pectin: 5.8±0.38 (Mean±SEM)
Difference	Total cholesterol: 0.00±0.23 p=1.00 (p-value calculated in Review Manager)
Notes	HDL measured and "no difference stated" but no data shown
Adverse effects	No adverse effects were noted, but participants had "great difficulty" consuming the full amount of the pectin, and thus consumed only 12g of the prescribed 15g per day.
Funding source	None stated

Reference	Schwab et al. 2006
Study design	Randomised, placebo-controlled, double-blind parallel trial
Objectives	To study the effects of sugar beet pectin or polydextrose on fasting and postprandial glycemia and fasting concentrations of serum total and lipoprotein lipids in middle-aged subjects with abnormal glucose metabolism.
Sample size	22 (control) and 22 (pectin) analysed; in the overall study which also examined an arm with polydextrose, total of 70 enrolled, 66 completed; no sample size calculations given
Participants	Mean age 52±8, normal liver, kidney, thyroid function, but all with abnormal glucose metabolism and mild-moderate hypercholesterolaemia.
Interventions	Consumption of a sweet drink containing no fibre, 16g sugar beet pectin or 16 g polydextrose consumed each day with main meals for 12 weeks.
Methods	Cholesterol and triglycerides determined using automated enzymatic colorimetric methods
Confounders	Controlled by measuring weight, BMI, glucose, cholesterol and nutrient intakes at baseline and throughout the study.
Results	Total cholesterol: control: 5.61±0.20 (baseline), 5.32±0.22 (end), sugar beet pectin: 5.71±0.23 (baseline), 5.54±0.15 (end) (Mean±SEM)
Difference	Total cholesterol +0.12±0.20 p=0.55 (p-value calculated in Review Manager)
Notes	Laboratory personnel also blind
Adverse effects	No adverse effects were noted.
Funding source	Danisco Ltd, Espoo, Finland

Reference	Sirtori et al. 2012
Study design	Randomised, double-blind, placebo-controlled parallel
Objectives	To evaluate the effect of plant protein in combination with soluble fibres on plasma total and LDL cholesterol concentrations

Sample size	25 (control) all completed; 25 (pectin) 20 completed; no sample size calculations given
Participants	Middle-aged, healthy hyper-cholesterolaemic people
Interventions	Two bars per day each containing 10g of either cellulose (placebo) or high DE apple pectin for four weeks
Methods	Cholesterol and triglycerides determined using automated enzymatic colorimetric methods
Confounders	Controlled by double blinding.
Results	Total cholesterol: Control: baseline: 7.04±0.18; end: 7.12±0.14 Pectin: baseline: 7.42±0.26; end: 7.03±0.24 (Mean±SEM)
Difference	Total cholesterol -0.47±0.19 p=0.01 (p-value calculated in Review Manager)
Notes	Multiple intervention arms in trial: casein±pectin, pea protein±pectin, lupin protein + cellulose, casein + oat fibre, pea protein + oat fibre. Chose casein±pectin as casein is the simplest vehicle.
Adverse effects	Minor gastrointestinal effects noted. Five subjects dropped out of pectin arm, whereas no subjects dropped out of control arm, suggesting side-effects.
Funding source	European Commission grant.

Reference	Stasse-Wolthuis et al. 1980
Study design	Randomised, controlled parallel trial, not blind
Objectives	To study the effect of dietary fibre from vegetables, fruits, bran or citrus pectin on serum lipids, faecal lipids and colonic function
Sample size	16 (control) 15 (pectin) analysed no sample size calculations given
Participants	Healthy, normal weight, normal BP, normal cholesterol adults aged 18-28
Interventions	Introduced fibre in 9g pectin desserts per day to be eaten with meals as part of a low-fibre diet, compared with low-fibre diet alone over 7.5 weeks.
Methods	Cholesterol was determined using a variant of the Liebermann-Burchard reaction.
Confounders	Controlled by providing all food to be consumed during the study, plus checking actual intake by weighing plus a questionnaire.
Results	Total cholesterol: change (control): +0.1± 0.09; (pectin): -0.34±0.09 (Mean±SEM)
Difference	Total cholesterol: -0.44±0.12 p=0.0002 (p-value calculated in Review Manager)
Notes	None
Adverse effects	No adverse effects were reported.
Funding source	Netherlands Heart Foundation grant

2.2.3 Quality assessment of individual studies

Brouns et al. (2012) is a study in 29 healthy, mildly hyper-cholesterolaemic people. The aim of the study was to examine the effect of different molecular weights and degrees of esterification (DE) of pectin on its cholesterol-lowering abilities. The different pectins trialed were high- and low-molecular weight pectins, as well as apple and citrus pectins at low and high degrees of esterification, and orange pulp fibre. The control used was cellulose. Participants ate any combination of cereal bars, fruit preparations and capsule to add to a total of 15 g pectin per day. To avoid double counting of the control arm by calculating multiple differences, a single intervention arm was chosen. We chose the high DE apple pectin as this was the most common type of pectin consumed naturally in the diet (citrus pectin is derived from orange peels which are not routinely eaten).

Cerda et al.(1988) is a double-blind, crossover trial in 27 healthy volunteers with hypercholesterolaemia. Participants were given 15 g per day of high DE citrus pectin in the form of 27 capsules per day, taken with three meals. The placebo was the same capsules filled with flour. The aim of the study was to analyse the effects of grapefruit pectin on cholesterol concentrations, without changing the diet or other lifestyle factors.

Challen et al. (1983) carried out a small study involving 11 young, healthy men. The aim of the study was to examine the effect of consumption of additional pectin or wheat bran on platelet function and haemostasis. Only six of the participants were in the pectin group. These men were given all foods during the study, and were randomised into two groups of three. Each group consumed either the provided control diet, or else the same diet with 36 g of pectin added each day in the form of a dry powder mixed with foods throughout the day. There was no placebo for the control group, meaning the risk of bias for this study is quite high. Furthermore, it is debatable whether the participants truly complied with the addition of such a large amount of pectin. In another supplement study in this review (Hillman et al. 1985), participants could not consume 15 g per day (see below). The article did not report the extent to which participants complied with the diet.

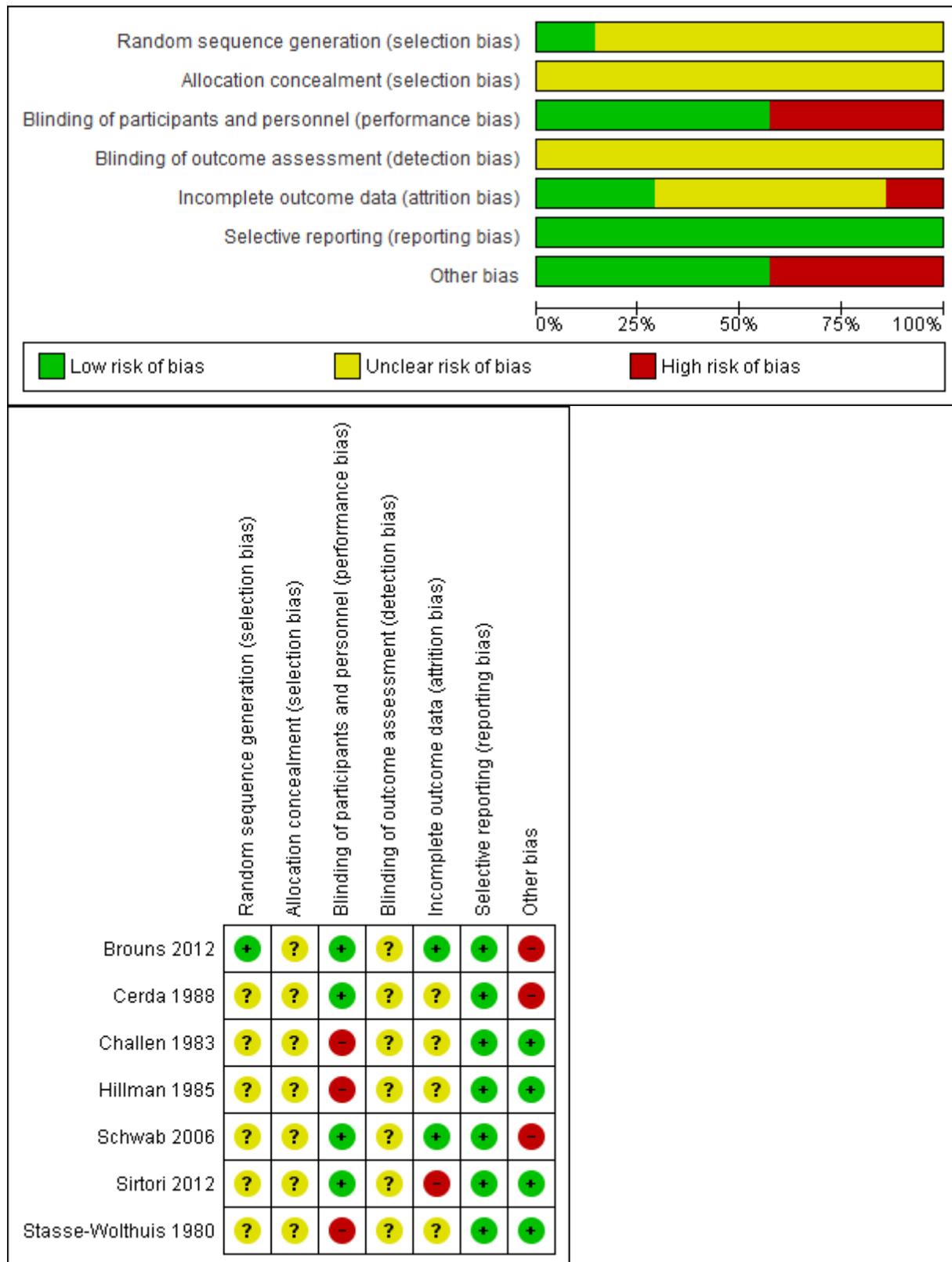
Hillman et al. (1985) is a crossover study involving 30 healthy volunteers, 10 of whom took part in the pectin intervention arm. The study looked at the effects of pectin, cellulose or lignin consumption on serum cholesterol concentrations. As in Challen et al. (1983), the pectin was provided as powder added to food consumed throughout the day. It is unclear whether the participants knew which intervention they were taking, but it is clear that no placebo was used. Thus the participants knew when they were in an intervention period and this may have affected their behaviour. Of note is that the participants could not consume the full 15 g per day of pectin that was originally prescribed for the trial. This was attributed to its gelling properties. The participants actually consumed 12 g of pectin per day.

Schwab et al. (2006) is a parallel study involving 66 middle-aged participants with abnormal glucose metabolism. The aim of the study was to examine the effects of sugar beet pectin or polydextrose on glycaemia and blood lipids. The participants were randomised into three groups (n= 22 analysed in each), who, in addition to nutritional counselling, consumed identical drinks containing sugar beet pectin, polydextrose or no soluble fibre (the polydextrose arm was excluded from the current review).

Sirtori et al. (2012) is a parallel study involving 175 participants randomised to receive a number of different protein/fibre combinations. The aim was to investigate the influence of lupin and pea proteins as well as fibres/fibre-rich food such as pectin and oats in combination and alone on blood cholesterol concentrations. Participants received two bars per day for four weeks, with casein being the control protein and cellulose being the control fibre. This design allowed comparison of the outcomes for the casein/cellulose group (n=25) with the casein/pectin group (n=20).

Stasse-Wolthuis et al. (1980) is a parallel study involving 62 young, healthy subjects with normal cholesterol concentrations. The study's aim was to examine the influence of dietary fibre from vegetables and fruits, bran or citrus pectin on serum lipids, faecal lipids and colonic functions in the context of a low-fibre diet. The participants were given all food to be consumed during the period of the study. After an initial 2.5 weeks on a low fibre diet, the subjects were randomised into four groups: low-fibre diet alone (n=16), high fibre diet (fruits and vegetables), low-fibre diet plus 9g citrus pectin (n=15), low-fibre diet plus wheat bran. The comparison selected for the current review was low fibre versus low fibre plus citrus pectin. While the allocation into the fruit and vegetable arm could not be concealed from participants, the control, citrus pectin and wheat bran interventions could have been concealed but were not blinded. Therefore, this study is liable to performance bias. The risk of bias assessment is shown in Figure 2. Studies which used placebos or placebo foods and were double-blind, and so were at low risk of performance bias, were classified as high quality studies (Brouns et al. 2012, Cerda et al. 1988, Schwab et al. 2006, Sirtori et al. 2012). Allocation concealment is not described. Four studies were regarded as having unclear attrition because the authors did not state whether there had been any dropouts (Figure 2). The 'other bias' column reflects which studies specifically stated that they had received funding from industry.

Figure 2 Risk of bias in the seven included studies



In order to see if there was a risk of publication bias, the included studies were mapped as a funnel plot around the average effect on total cholesterol concentration. It appears that the risk of publication bias is not severe, although there are few studies (Figure 3).

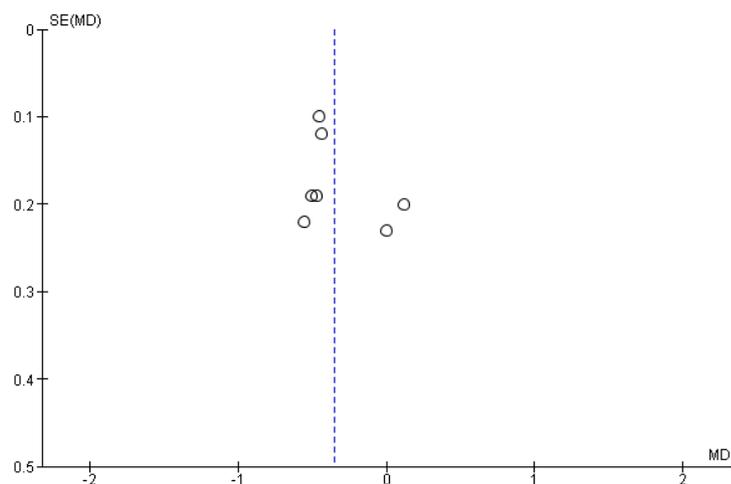


Figure 3 Funnel plot of all included studies

2.3 Summary of evidence

From the initial 115 individual studies identified through the search strategy, only seven met all the criteria. These studies were published between 1980 and 2012. None of the studies was large, with participant numbers ranging from 6 to 29 in the cross-over studies and 31 to 44 in the parallel studies (control and intervention groups combined). The studies ranged in their design (three parallel, four cross-over) and the type of intervention (pectin in capsules, pectin rich food, pectin powder added to food or purified pectin as an ingredient in foods).

To provide a convenient way of viewing the range of findings from the included studies, *Figure* illustrates the relationship (mean and standard error) between total cholesterol concentrations and daily amount of pectin consumed.

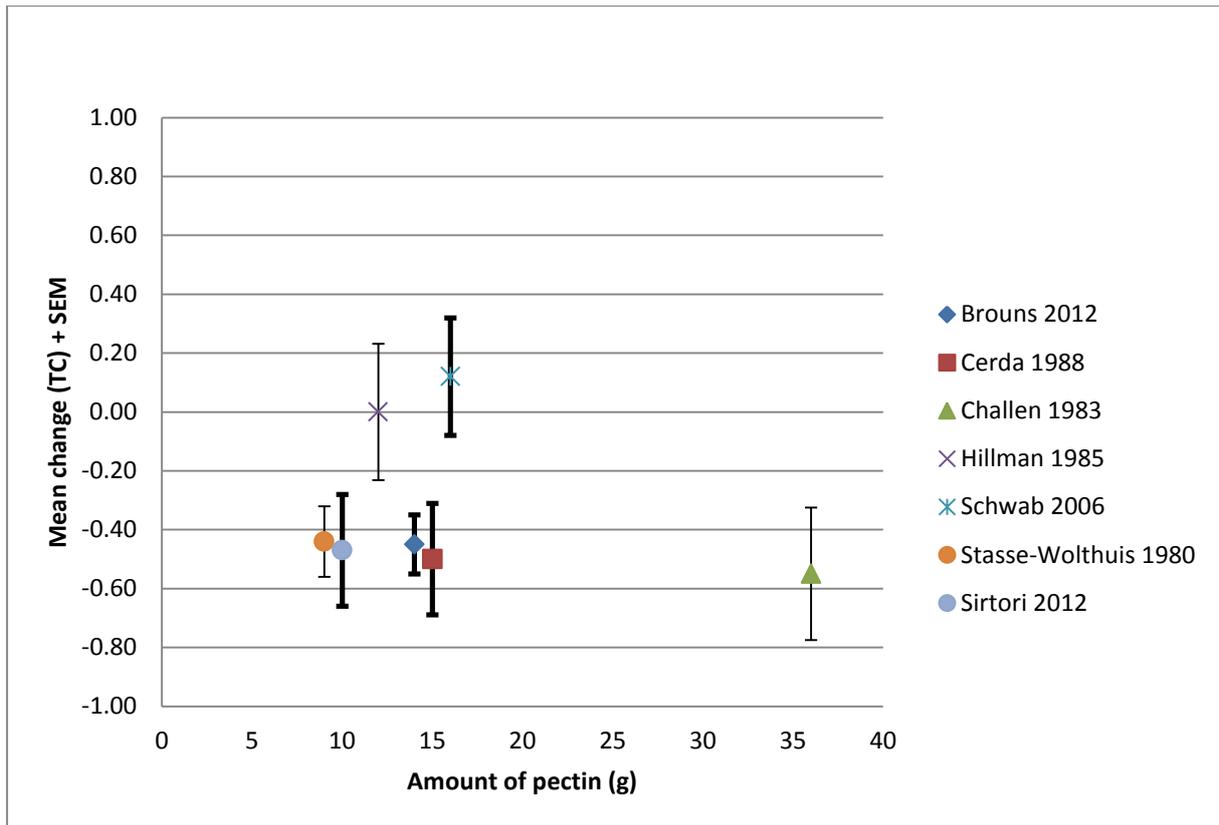


Figure 4 Scatterplot of change in total cholesterol against daily amount of pectin

The amount of pectin consumed per day (X-axis) is plotted against the mean change and standard error in total cholesterol in the intervention vs control group (Y-axis). High quality studies are displayed with bold error bars.

Of the seven included studies, four were considered to be high quality (Brouns et al. 2012, Cerda et al. 1988, Schwab et al. 2006, Sirtori et al. 2012). These studies used a placebo during the intervention phase, thus controlling for potential behavioural changes associated with the knowledge of group allocation. One study found a non-significant increase in total cholesterol concentration (Schwab et al. 2006). The other three studies found effect sizes between -0.55 and 0 mmol/L. The remaining three studies were not blinded, and were thus at risk of bias in their outcomes, even though the measurement itself (blood cholesterol concentrations) is conducted mechanically and is not subject to interpretation issues. For the most part, all the studies made an effort to control the diet through either provision of foods or advice on healthy eating provided before the study started. All studies asked participants to provide information, usually in the form of food diaries, to ensure food intake was similar between groups and throughout the study.

In order to determine if there was an effect overall from all included studies, we undertook a meta-analysis (see Figure 5). All studies together gave an overall effect size 0.36 mmol/L [95% CI: -0.52, -0.19] mmol/L, $p < 0.0001$.

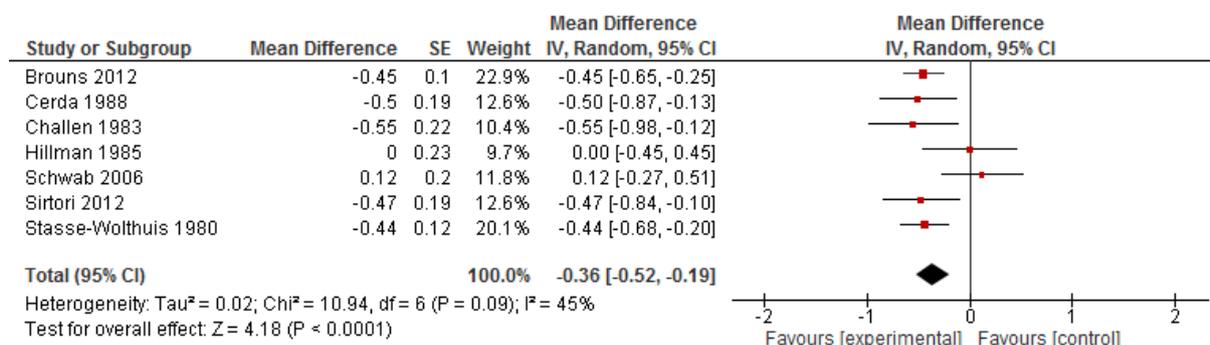


Figure 5 Forest plot of included studies

2.3.1 High quality versus low quality studies

Inclusion of high quality studies alone still resulted in a highly significant difference in total cholesterol (-0.34mmol/L [95% CI:-0.60, -0.09], p=0.008). One of the four high quality studies (Schwab et al. 2006) failed to show a statistically significant difference. The low quality studies also showed a significant result (-0.36mmol/L [95% CI: -0.64, -0.08], p=0.01 (see Table 3).

Table 3 Subgroup analyses by quality and source of funding

Subgroup		Mean Difference (mmol/L)	P
Quality	<i>High quality</i> (Brouns et al. 2012; Cerda et al. 1988; Schwab et al.2006; Sirtori et al. 2012)	-0.34 [95% CI: -0.60, -0.09]	0.008
	<i>Low quality</i> (Challen et al. 1983, Hillman et al. 1985, Stasse-Wolthuis et al. 1980)	-0.36 [95% CI: -0.64, -0.08]	0.01
Source of funding	<i>Industry</i> (Brouns et al. 2012; Cerda et al. 1988; Schwab et al. 2006)	-0.30 [95% CI: -0.64, 0.04]	0.09
	<i>Independent/not stated</i> Challen et al. 1983; Hillman et al. 1985; Sirtori et al. 2012; Stasse-Wolthuis et al. 1980)	-0.39 [95% CI:-0.59, -0.20]	<0.0001

2.3.2 Industry funded versus independent studies

The industry-funded studies (Brouns et al. 2012; Cerda et al. 1988; Schwab et al. 2006) gave a slightly reduced total effect size when compared with the total overall effect size. The independently-funded studies (including studies which did not state any funding source) (Challen et al. 1983, Hillman et al. 1985, Sirtori et al. 2012, Stasse-Wolthuis et al. 1980) found a slightly larger effect size. (-0.39 [95% CI:-0.59, -0.20], p<0.0001). All of the industry-funded studies were classified as high quality, whereas one of four independent studies was classified as high quality.

2.3.3 Studies in normocholesterolaemics vs hypercholesterolaemics

There was only one study using a group of participants with a normal mean blood total cholesterol concentration (Stasse-Wolthuis et al. 1980) and was classified as a low quality

study. The effect was greater in this study compared with the six studies in people with abnormal cholesterol concentrations. The six studies in groups with elevated blood total cholesterol concentrations showed an overall effect of -0.33 mmol/L [95% CI:-0.54, --0.12], $p=0.002$.

3 Weight of evidence

Five out of seven studies reported a decrease in total blood cholesterol concentrations following pectin consumption. Of the three low-quality studies, two found a decrease in total cholesterol (Challen et al. 1983; Stasse-Wolthuis et al. 1980) and one found no differences (Hillman et al. 1985). Of the high quality studies, although three reported a reduction in blood total cholesterol (Brouns et al. 2012; Cerda et al. 1988; Sirtori et al. 2012), one high quality study reported a non-significant increase in total cholesterol concentrations (Schwab et al. 2006). Of note, however, is that of the seven studies, two of them failed to find a statistically significant difference in blood total cholesterol concentrations.

Furthermore, all studies except that by Stasse-Wolthuis et al. (1980) were conducted in populations with a mean total cholesterol concentration greater than ≥ 5.5 mmol/L. The one study in people with normal cholesterol concentrations reported a slightly larger effect although it was of low quality and tested the smallest amounts of pectin (Stasse-Wolthuis et al. 1980).

For a food-health relationship to be substantiated there has to be a consistency of effect across high quality studies. However, owing to the high risk of bias in nearly half of the studies and the small numbers of participants in most studies, the GRADE rating for the relationship is 'Moderate' (Appendix 3).

3.1 Assessment of body of evidence

3.1.1 Consistency of relationship

There was moderate heterogeneity in the effect of pectin on total blood cholesterol concentrations ($I^2 = 45\%$). However, studies using similar amounts of pectin do not always report an effect and therefore we rate the consistency as 'Moderate'.

3.1.2 Causality

Randomised controlled trials are a strong design for inferring causality. There appears to be a relationship between consumption of pectin and total blood cholesterol. However, our degree of certainty in this causality is 'Moderate'.

3.1.3 Plausibility

There is a plausible physiological mechanism by which pectin might lower cholesterol, namely by disrupting the enterohepatic recirculation of bile salts. Bile salts in bile are secreted into the duodenum in response to the presence of food in the stomach and resorbed from the distal end of the ileum. This mechanism is similar to that observed with daily oral administration of cholestyramine (an ion exchange resin) (Nazir et al. 1972). Soluble pectin fibres might exhibit gel-like properties and sequester bile salts. This loss of cholesterol in the form of bile salts, if greater than the rate of bile acid synthesis in the liver, would lead to a reduced blood cholesterol level as cholesterol is removed from the blood to compensate for the loss of bile acid salts.

Since *in vitro* binding studies have shown that 2% (w/v) cholestyramine can bind 82% of a diluted human bile solution containing 8 mmol/L bile salts, 1.4 mmol/L phospholipids and 0.6 mmol/L cholesterol, cholestyramine's proposed mode of action and efficacy *in vivo* seems well-founded. In contrast, an equivalent amount of pectin was only able to bind 6% of the diluted human bile solution under the same conditions (Lairon et al. 1985).

3.2 Applicability to Australia and New Zealand

3.2.1 Intake required for effect

The studies tested daily intakes of pectin ranging between 9 g and 36 g. The average intake of total fibre in adults 19 years and older in Australia is 22.9 g/day (ABS 2014) and 20.3 g/day in New Zealanders aged 15 years and older (University of Otago and Ministry of Health 2011). There is little information about the pectin content of food. The AUSNUT database does not contain any data for this component.

A recent UK survey analysed fruit and vegetables for total fibre by the AOAC method and non-starch polysaccharides (NSP) by the Englyst method (UK Department of Health 2013). Pectin is one type of fibre captured by the Englyst method. Microwaved frozen peas contained 4.5 g NSP/100 g, baked beans in tomato sauce 3.8 g/100 g, carrots, green beans broccoli, corn kernels, cabbage and tomato puree contained 2-3 g NSP/100 g. The pectin content would be lower than the NPS content listed. Therefore it is unlikely that the average person in Australia and New Zealand could achieve the intakes of pectin tested in these studies (9-36 g/day). As there is no apparent dose-response relationship across the range tested, it is not possible to extrapolate the data to lower intakes which might be achievable.

3.2.2 Target population

Although the studies were all carried out overseas, they were all done in countries with similar dietary habits to those in Australia and New Zealand. Therefore, the outcome would apply to Australia and New Zealand. No studies were identified in non-Caucasian populations.

There were no studies in children.

There was only one, low quality, study conducted in people with normal cholesterol concentrations. The high quality studies were all conducted in people with elevated cholesterol concentrations.

3.2.3 Extrapolation from supplements

All the studies except one were carried out using foods containing pectin, either naturally or added into food to create a pectin-rich food product. Two studies were included that were purely pectin powder added to food, as this was seen as a very similar route of ingestion to pectin-enriched food. One study was included in which participants were given pectin in capsules. There were no significant differences in the outcomes between pectin-enriched foods and pectin added to foods or taken as capsules at the time of consumption.

3.2.4 Adverse effects

A common adverse effect reported was gastrointestinal discomfort. This discomfort included bloating, flatulence and some cramping. These adverse effects were not universally recorded, although it is not clear whether participants were universally questioned about them.

4 Conclusion

Based on the evidence from high quality studies it was not possible to establish with a high degree of certainty a relationship between increased pectin intake and reduced blood total cholesterol concentrations. FSANZ has rated the evidence for the relationship between pectin consumption and blood total cholesterol concentrations as “Moderate”.

Acknowledgment

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Appendix 1: Search terms

The following search strategy was used to identify studies for including in the review:

PubMed

((pectins[MeSH Terms]) OR pectin*) OR pectic polysaccharides

AND

(cholesterol[MeSH Terms] OR cholesterol OR lipoproteins, low density[MeSH Terms] OR (low density lipoprotein or LDL) OR hypercholesterolemia[MeSH Terms] OR (hypercholesterolemia or hypercholesterolaemia))

AND

("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR randomi*ed[Title/Abstract] OR placebo[Title/Abstract] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract])

EMBASE

1	exp pectin/ or pectin*.mp. or pectic polysaccharides.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	10286	Advanced
2	exp cholesterol/ or cholesterol.mp. or exp low density lipoprotein/ or (low density lipoprotein or LDL).mp. or exp hypercholesterolemia/ or (hyperc holesterolemia or hypercholesterolaemia).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	352676	Advanced
3	1 and 2	426	Advanced
4	limit 3 to (randomized controlled trial or controlled clinical trial)	19	Advanced
5	(randomi*ed or placebo or randomly or trial or groups).ti,ab.	2342097	Advanced
6	3 and 5	100	Advanced
7	4 or 6	107	Advanced

Cochrane

#1 MeSH descriptor: [Pectins] explode all trees

#2 MeSH descriptor: [Cholesterol] explode all trees

#3 MeSH descriptor: [Lipoproteins, LDL] explode all trees

#4 MeSH descriptor: [Hypercholesterolemia] explode all trees

#5 #1 OR pectin* OR pectic polysaccharides

#6 #2 OR #3 OR #4 OR cholesterol OR low density lipoprotein OR LDL OR hypercholesterolemia OR hypercholesterolaemia

#7 "randomised controlled trial" OR "controlled clinical trial" OR randomi*ed OR placebo OR randomly OR trial OR groups

#8 #5 AND #6 AND #7

Appendix 2: Studies excluded at full text review

Author	Reference	Reason
Aller 2004	(Aller <i>et al.</i> , 2004)	Intervention was a mix of soluble fibres, not pectin alone
Bell 1990	(Bell <i>et al.</i> , 1990)	Intervention was a mix of soluble fibres, not pectin alone, plus control was inadequate.
Davidson 1998	(Davidson <i>et al.</i> , 1998)	Intervention was a mix of soluble fibres, not pectin alone
de Queiroz 2012	(de Queiroz <i>et al.</i> , 2012)	Intervention whole food with mixed fibres
Frape 1995	(Frape and Jones, 1995)	Intervention was a mix of soluble fibres, not pectin alone, intervention 4 days only.
Haskell 1992	(Haskell <i>et al.</i> , 1992)	Intervention was a mix of soluble fibres, not pectin alone
Hillman 1986	(Hillman <i>et al.</i> , 1986)	Study on bile acids, not blood cholesterol
Hoffman 1999	(Hoffmann <i>et al.</i> , 1999)	Study duration 4 days only
Hosobuchi 1999	(Hosobuchi <i>et al.</i> , 1999)	Intervention was a mix of soluble fibres, not pectin alone
Hunninghake 1994	(Hunninghake <i>et al.</i> , 1994)	Intervention was a mix of soluble fibres, not pectin alone
Jensen 1993	(Jensen <i>et al.</i> , 1993)	Intervention was a mix of soluble fibres, not pectin alone
Jensen 1997	(Jensen <i>et al.</i> , 1997)	Intervention was a mix of soluble fibres, not pectin alone
Judd 1982	(Judd and Truswell, 1982)	No control group
Knopp 1999	(Knopp <i>et al.</i> , 1999)	Intervention was a mix of soluble fibres, not pectin alone
Liebermeister 1980	(Liebermeister and Toluipur, 1980)	Intervention was a mix of soluble fibres, not pectin alone
Mahalko 1984	(Mahalko <i>et al.</i> , 1984)	Intervention was a mix of soluble fibres, not pectin alone
Palmer	(Palmer and Dixon, 1966)	Background diet not provided
Pirich 1992	(Pirich <i>et al.</i> , 1992)	Intervention was a mix of soluble fibres, not pectin alone
Raymond 1997	(Raymond <i>et al.</i> , 1977)	Intervention was a mix of soluble fibres, not pectin alone
Sheehan 1997	(Sheehan <i>et al.</i> , 1997)	Study sequential not cross-over
Singh 1992	(Singh <i>et al.</i> , 1992)	Inadequate control, different diets between control and intervention groups, intervention was a whole food with mixed fibres
Tinker 1991	(Tinker <i>et al.</i> , 1991)	Intervention was a whole food with mixed fibres
Veldman 1997	(Veldman <i>et al.</i> , 1997)	Cholesterol data reported at % change from baseline but mean baseline concentration not given(all subjects had total cholesterol concentration >5.2mmol/L) – author could not be contacted

Appendix 3: GRADE summary of findings table

Question: Is there a relationship between pectin and blood total cholesterol?

Source: FSANZ systematic review of evidence

Quality Assessment of body of evidence							Participants		Mean difference mmol/L (95% CI)	Quality (degree of certainty in relationship)
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Considerations	Parallel studies	Cross-over studies		
Total cholesterol (all studies)										
7 ¹	RCTs	Moderate ²	Moderate	None	Low	None	120	72	-0.36 [-0.52, -0.19]	⊕⊕⊕ Moderate
Total cholesterol (high quality studies)										
4	RCTs	Low	Moderate	None	Low	None	89	56	-0.34 [-0.60, -0.09]	⊕⊕⊕ Moderate
Total cholesterol (normocholesterolaemic participants)										
1	RCT	High ³	N/A	None	Low	Consistent results with hypercholesterolaemic other group; but classified as a low quality study	31	none	-0.44 [-0.68, -0.20]	⊕⊕ Low
Total cholesterol (hypercholesterolaemic participants)										
6	RCTs	Moderate	Moderate	None	Moderate ⁴	None	89	72	-0.33 [-0.54, -0.12]	⊕⊕⊕ Moderate

N/A not applicable

¹ The seven studies tested 9-36 g pectin per day

² Three out of seven studies not blinded

³ Low quality study, not blinded

⁴ Two out of six studies had wide confidence intervals