HAROKOPIO UNIVERSITY
SCHOOL OF HEALTH SCIENCE AND EDUCATION
DEPARTMENT OF NUTRITION AND DIETETICS
APPLIED NUTRITION AND DIETETICS
CLINICAL NUTRITION

DIET AND CARDIOVASCULAR DISEASE RISK AMONG INDIVIDUALS WITH FAMILIAL HYPERCHOLESTEROLEMIA: SYSTEMATIC REVIEW AND META-ANALYSIS

MSc THESIS

Fotios Barkas

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ΧΑΡΟΚΟΠΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ
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ΔΙΠΛΩΜΑΤΙΚΗ ΔΙΑΤΡΙΒΗ

Φώτιος Μπάρκας

ΑΘΗΝΑ 2020

Τριμελής Εξεταστική Επιτροπή

ΔΗΜΟΣΘΕΝΗΣ ΠΑΝΑΓΙΩΤΑΚΟΣ (Επιβλέπων)
Καθηγητής Βιοστατιστικής - Επιδημιολογίας,
Τμήμα Διαιτολογίας - Διατροφής,
Χαροκόπειο Πανεπιστήμιο

ΕΥΑΓΓΕΛΟΣ ΛΥΜΠΕΡΟΠΟΥΛΟΣ
Αναπληρωτής Καθηγητής Παθολογίας,
Τμήμα Ιατρικής,
Πανεπιστήμιο Ιωαννίνων

ΤΖΩΡΤΖΗΣ ΝΟΜΙΚΟΣ
Επίκουρος Καθηγητής Βιοχημείας,
Τμήμα Διαιτολογίας - Διατροφής,
Χαροκόπειο Πανεπιστήμιο

Ο Φώτιος Μπάρκας δηλώνω υπεύθυνα ότι:

1) Είμαι ο κάτοχος των πνευματικών δικαιωμάτων της πρωτότυπης αυτής εργασίας και από όσο γνωρίζω η εργασία μου δε συκοφαντεί πρόσωπα, ούτε προσβάλει τα πνευματικά δικαιώματα τρίτων.

2) Αποδέχομαι ότι η ΒΚΠ μπορεί, χωρίς να αλλάξει το περιεχόμενο της εργασίας μου, να τη διαθέσει σε ηλεκτρονική μορφή μέσα από τη ψηφιακή Βιβλιοθήκη της, να την αντιγράψει σε οποιοδήποτε μέσο ή/και σε οποιοδήποτε μορφότυπο καθώς και να κρατά περισσότερα από ένα αντίγραφα για λόγους συντήρησης και ασφάλειας.

Στους γονείς μου

Στην Κωνσταντίνα και στη Δέσποινα

ΠΡΟΛΟΓΟΣ

Η πραγματοποίηση της παρούσας ανασκόπησης δεν θα ήταν δυνατή χωρίς τη διαρκή καθοδήγηση του επιβλέποντα της μεταπτυχιακής διατριβής κ. Δημοσθένη Παναγιωτάκου, Καθηγητή Βιοστατιστικής και Επιδημιολογίας, του τμήματος Διαιτολογίας και Διατροφής, του Χαροκοπείου Πανεπιστημίου και του κ. Τζώρτζη Νομικού, Επίκουρου Καθηγητή Βιοχημείας του τμήματος Διαιτολογίας και Διατροφής, του Χαροκοπείου Πανεπιστημίου, τις χρήσιμες υποδείξεις τους, τις πρωτότυπες ιδέες τους, καθώς και την εμπιστοσύνη και ηθική υποστήριξή τους. Η συνεργασία μας αποτελεί εξαιρετική τιμή για μένα και τους ευχαριστώ θερμά. Ιδιαίτερα ευχαριστώ το μέλος της τριμελούς επιτροπής κ. Ευάγγελο Λυμπερόπουλο, Αναπληρωτή Καθηγητή Παθολογίας της Ιατρικής Σχολής, του Πανεπιστημίου Ιωαννίνων, για τον πολύτιμο χρόνο που διέθεσε για την παρούσα μεταπτυχιακή διατριβή.

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Ιωάννινα, Ιούνιος 2020

Φώτιος Μπάρκας

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ΠΕΡΙΛΗΨΗ

Εισαγωγή: Αν και η δίαιτα χαμηλής περιεκτικότητας σε λιπαρά/χοληστερόλη και οι φυτικές στερόλες/στανόλες προτείνονται σε παιδιά και ασθενείς με οικογενή υπερχοληστερολαιμία, δεν υπάρχουν αρκετά δεδομένα από τυχαιοποιημένες κλινικές μελέτες που να επιβεβαιώνουν τις συστάσεις αυτές.

Σκοπός: Η διερεύνηση της επίδρασης της υπολιπιδαιμικής δίαιτας και άλλων διαιτητικών παρεμβάσεων στην επίπτωση της καρδιαγγειακής νόσου ή θνητότητας και στο λιπιδαιμικό προφίλ ατόμων με οικογενή υπερχοληστερολαιμία.

Μεθοδολογία έρευνας: Αναζητήθηκαν σχετικές μελέτες από τις βάσεις δεδομένων US National Library of Medicine National Institutes of Health Metabolism Trials Register και clinicaltrials.gov χρησιμοποιώντας τις εξής λέξεις-κλειδιά: δίαιτα, διαιτητικές, φυτικές στερόλες, στανόλες, ωμέγα-3 λιπαρά οξέα, ίνες και οικογενή υπερχοληστερολαιμία.

Κριτήρια επιλογής: Συμπεριελήφθησαν τυχαιοποιημένες κλινικές μελέτες που μελέτησαν την επίδραση της υπολιπιδαιμικής δίαιτας και άλλων διαιτητικών παρεμβάσεων σε παιδιά και ενήλικες με οικογενή υπερχοληστερολαιμία.

Σύνθεση και ανάλυση δεδομένων: Δύο συγγραφείς αξιολόγησαν ανεξάρτητα την επιλεξιμότητα των μελετών και τον κίνδυνο μεροληψίας, ενώ ένας εξήγαγε τα δεδομένα, με ανεξάρτητη επαλήθευση της εξαγωγής δεδομένων από έναν άλλο ερευνητή.

Αποτελέσματα: Συμπεριλήφθηκαν συνολικά 17 δοκιμές με 376 συμμετέχοντες σε 8 ομάδες σύγκρισης. Ο κίνδυνος μεροληψίας για τις περισσότερες από τις παραμέτρους που χρησιμοποιήθηκαν για την εκτίμησή του ήταν χαμηλός ή ασαφής. Η επίπτωση ή θνητότητα καρδιαγγειακής νόσου δεν αξιολογήθηκαν σε καμία από τις μελέτες. Σχετικά με το λιπιδαιμικό προφίλ των ασθενών, παρατηρήθηκε σημαντική διαφορά για τις ακόλουθες συγκρίσεις και αποτελέσματα: τα ωμέγα-3 λιπαρά οξέα μείωσαν τα επίπεδα των τριγλυκεριδίων (μέση διαφορά [MD]: -0,27 mmol/L, διάστημα εμπιστοσύνης 95% [CI]: -0,47 έως -0,07, p<0,01) συγκριτικά με το εικονικό φάρμακο. Παρατηρήθηκε μια στατιστικά μη σημαντική τάση για τη μείωση των επιπέδων της ολικής χοληστερόλης (MD: -0,34, 95% CI: -0,68 έως 0, mmol/L, p=0,05) και της χοληστερόλης των χαμηλής πυκνότητας λιποπρωτεϊνών (MD: -0,31, 95% CI: -0,61 έως 0, mmol/L, p=0,05). Σε σύγκριση με την υπολιπιδαιμική δίαιτα, η επιπρόσθετη

κατανάλωση φυτικών στανολών μείωσαν τα επίπεδα της ολικής χοληστερόλης (MD: -0,62 mmol/L, 95% CI: -1,13 έως -0,11, p=0,02) και της χοληστερόλης των χαμηλής πυκνότητας λιποπρωτεϊνών (MD: -0,58 mmol/L, 95% CI: -1,08 έως -0,09, p=0,02). Το ίδιο παρατηρήθηκε και με τις φυτικές στερόλες (MD: -0,46 mmol/L, 95% CI: -0,76 έως -0,17, p<0,01 για τη χοληστερόλη και MD: -0,45 mmol/L, 95% CI: -0,74 έως -0,16, p<0,01 για τη χοληστερόλη των χαμηλής πυκνότητας λιποπρωτεϊνών). Δεν παρατηρήθηκε σημαντική ετερογένεια μεταξύ των μελετών που συμπεριελήφθησαν σε αυτές τις αναλύσεις.

Συμπεράσματα: Οι διαθέσιμες κλινικές μελέτες επιβεβαιώνουν ότι η προσθήκη των φυτικών στερολών ή στανολών στην υπολιπιδαιμική δίαιτα μειώνει τα επίπεδα της χοληστερόλης σε άτομα με οικογενή υπερχοληστερολαιμία. Αντίθετα, η χορήγηση ωμέγα-3 λιπαρών οξέων μειώνει αποτελεσματικά τα τριγλυκερίδια και ενδεχομένως να μειώνει και τη χοληστερόλη των ασθενών αυτών. Απαιτούνται επιπρόσθετες μελέτες για τη διερεύνηση της αποτελεσματικότητας της δίαιτας χαμηλής περιεκτικότητας σε λιπαρά/χοληστερόλη και της προσθήκης σόγιας ή διαιτητικών ινών σε άτομα με οικογενή υπερχοληστερολαιμία.

ABSTRACT

Background: Although a cholesterol-lowering diet and the addition of plant sterols and stanols are suggested for the lipid management of children and adults with familial hypercholesterolemia, there is limited evidence evaluating such interventions in this population.

Objectives: To investigate the impact of cholesterol-lowering diet and other dietary interventions on the incidence or mortality of cardiovascular disease and lipid profile of patients with familial hypercholesterolemia.

Search methods: Relevant trials were identified by searching US National Library of Medicine National Institutes of Health Metabolism Trials Register and clinicaltrials.gov.gr using the following terms: diet, dietary, plant sterols, stanols, omega-3 fatty acids, fiber and familial hypercholesterolemia.

Selection criteria: Randomized controlled trials evaluating the effect of cholesterol-lowering diet or other dietary interventions in children and adults with familial hypercholesterolemia were included.

Data collection and analysis: Two authors independently assessed the trial eligibility and bias risk and one extracted the data, with independent verification of data extraction by a colleague.

Results: A total of 17 trials were finally included, with a total of 376 participants across 8 comparison groups. The included trials had either a low or unclear bias risk for most of the parameters used for risk assessment. Cardiovascular incidence or mortality were not evaluated in any of the included trials. Among the planned comparisons regarding patients' lipidemic profile, a significant difference was noticed for the following comparisons and outcomes: omega-3 fatty acids reduced triglycerides (mean difference [MD]: -0.27 mmol/L, 95% confidence interval [CI]: -0.47 to -0.07, p<0.01) when compared with placebo. A non-significant trend towards a reduction in subjects' total cholesterol (MD: -0.34, 95% CI: -0.68 to 0, mmol/L, p=0.05) and low-density lipoprotein cholesterol (MD: -0.31, 95% CI: -0.61 to 0, mmol/L, p=0.05) was noticed. In comparison with cholesterol-lowering diet, the additional consumption of plant stanols decreased total cholesterol (MD: -0.62 mmol/l, 95% CI: -1.13 to -0.11, p=0.02) and low-

density lipoprotein cholesterol (MD: -0.58 mmol/l, 95% CI: -1.08 to -0.09, p=0.02). The same was by plant sterols (MD: -0.46 mmol/l, 95% CI: -0.76 to -0.17, p<0.01 for cholesterol, and MD: -0.45 mmol/l, 95% CI: -0.74 to -0.16, p<0.01 for low-density lipoprotein cholesterol). No heterogeneity was noticed among the studies included in these analyses.

Conclusions: Available trials confirm that the addition of plant sterols or stanols has a cholesterol-lowering effect on such individuals. On the other hand, supplementation with omega-3 fatty acids effectively reduces triglycerides and might have a role in lowering the cholesterol of patients with familial hypercholesterolemia. Additional studies are needed to investigate the effectiveness of a cholesterol-lowering diet or the addition of soya protein and dietary fibers to a cholesterol-lowering diet in familial hypercholesterolemia.

PICTURES

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ABBREVIATIONS

95% CI	95% Confidence intervals
ACS	Acute coronary syndrome
AHA	American Heart Association
Apo	Apolipoprotein
ASCVD	Atherosclerotic cardiovascular disease
BP	Blood pressure
CETP	Cholesteryl ester transfer protein
CHD	Coronary heart disease
CV	Cardiovascular
CVD	Cardiovascular disease
DASH	Dietary approaches to stop hypertension
DHA	Docosahexaenoic acid
DLCN	Dutch lipid clinic network
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
EPA	Eicosapentaenoic acid
ESC/EAS	European society of cardiology/European atherosclerosis society
FDA	Food and drug administration
FH	Familial hypercholesterolemia
GI	Glycemic index
GL	Glycemic load
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
HR	Hazard ratio
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
Lp(a)	Lipoprotein (a)
MetS	Metabolic syndrome
MD	Mean difference
MI	Myocardial infarction
MUFAs	Monounsaturated fats
non-HDL-C	Non-high-density lipoprotein cholesterol
OR	Odds ratio
PAD	Peripheral artery disease
PCSK9	Proprotein convertase subtilisin kexin 9
PUFAs	Polyunsaturated fats
RCTs	Randomized controlled trials
RR	Relative risk
SE	Standard error
SMD	Standardized mean difference

TC	Total cholesterol
TG	Triglycerides
TRLs	Triglyceride-rich lipoproteins
US	United States of America
VLDL	Very-low-density lipoprotein
WHO	World health organization

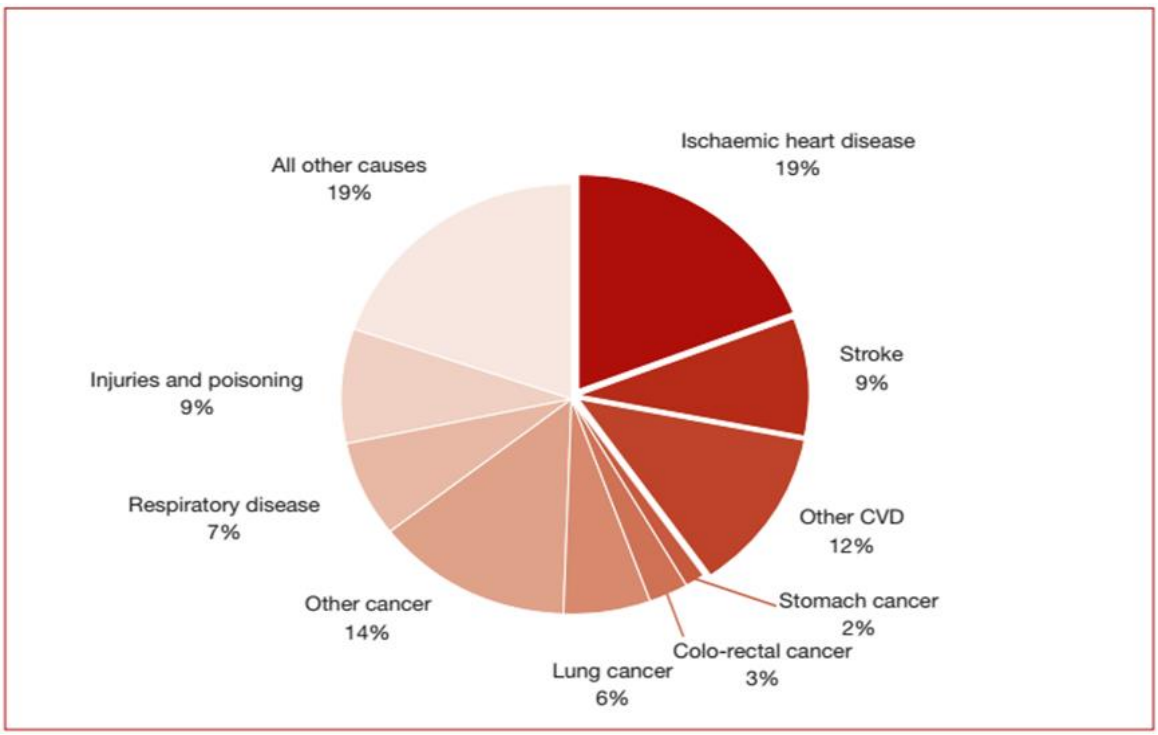
CHAPTER 1 INTRODUCTION

1.1 Epidemiology of cardiovascular disease

Cardiovascular disease (CVD) is the most common disease in the general population, affecting the majority of adults aged ≥60 years old.(WHO, 2018) According to the most recent report of the World Health Organization (WHO), 30% of 56.9 million deaths worldwide in 2016 were caused by coronary heart disease (CHD) and stroke (15.2 million deaths).(WHO, 2018) In Europe and United States of America (US), CVD is the leading cause of mortality.(Benjamin et al., 2019; Timmis et al., 2018) In Europe, CVD accounts for over 3.9 million annual deaths, corresponding to a proportion of 45% of all deaths.(Timmis et al., 2018) In men, CVD is responsible for 40% of all deaths (1.8 million deaths), whereas the corresponding mortality rate is 49% (2.1 million deaths) in women.(Timmis et al., 2018) On the contrary, cancer, the second cause of death in Europe, accounts for under 1.1 million deaths (24%) in men and under 900,000 deaths (20%) in women respectively (Figure 1A and Figure 1B).(Timmis et al., 2018)

The burden of CVD mortality varies across European countries.(Timmis et al., 2018) CVD prevalence is higher in Central and Eastern European countries compared with Northern, Southern and Western countries.(Timmis et al., 2018) Within the European Union, the CVD mortality rate ranges from 23% in France to 60% in Bulgaria among men, while in women, the burden ranges from 25% in Denmark to 70% in Bulgaria.(Timmis et al., 2018) Greece is among the European countries with intermediate CVD burden. Of the 116,669 registered deaths in 2012, CVD accounted for 43% of those (49,716 deaths).(Timmis et al., 2018)

Atherosclerotic cardiovascular disease (ASCVD) is comprised of CHD, stroke and peripheral artery disease (PAD).(Timmis et al., 2018) The former is the leading cause of mortality in Europe, accounting for 862,000 deaths annually (19% of all deaths) among men and 877,000 deaths (20%) among women each year.(Timmis et al., 2018) Stroke is the second most common cause of death in Europe, accounting for 405,000 deaths (9%) in men and 583,000 (13%) deaths in women annually (Figures 1A and 1B).(Timmis et al., 2018) Similarly, CHD and stroke were the leading causes of ASCVD mortality in Greece accounting for 11,803 and 15,868 deaths in 2012, respectively.(Timmis et al., 2018)



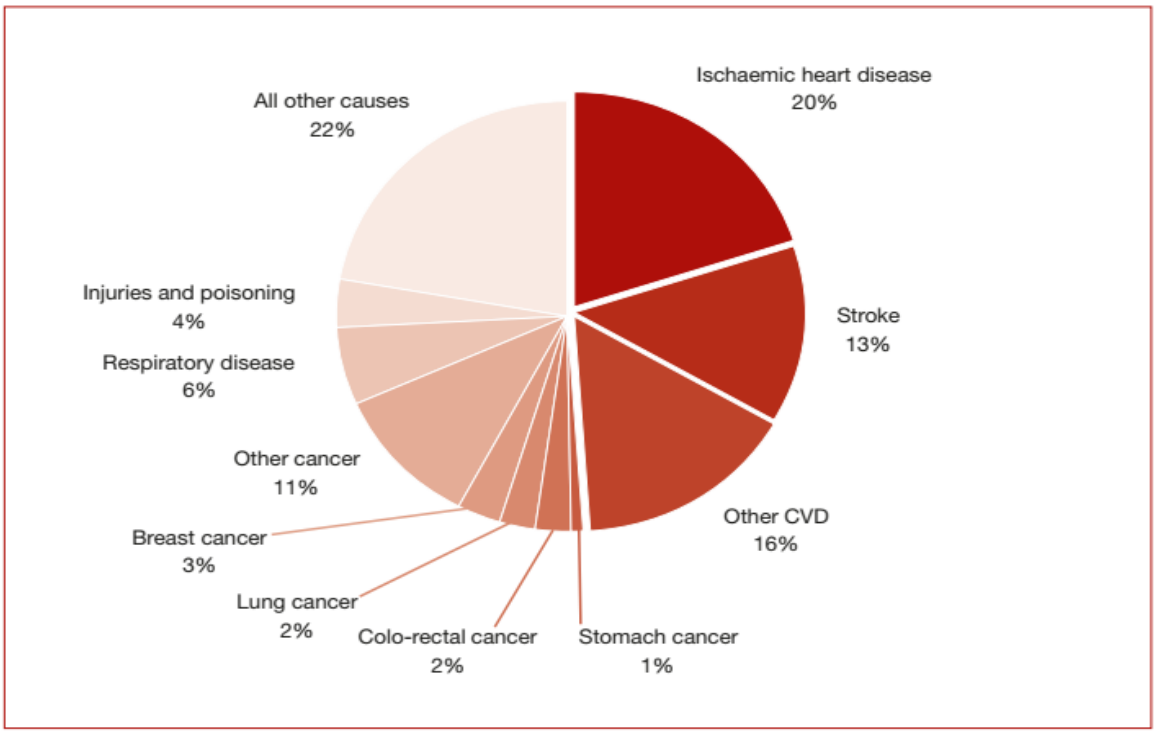


Figure 1B Mortality causes in women, latest available year, Europe

1.2 Risk factors for atherosclerotic cardiovascular disease

1.2.1 Prevalence of risk factors for atherosclerotic cardiovascular disease

Many individuals in the general population have one or more cardiovascular (CV) risk factors and over 90% of ASCVD events occur in individuals with at least one risk factor.(Stamler et al., 1999; Vasan et al., 2005; Yusuf et al., 2004) The 5 leading modifiable risk factors (hypercholesterolemia, diabetes mellitus [DM], hypertension, obesity, and smoking) account for more than half of CV mortality.(S. A. Patel, Winkel, Ali, Narayan, & Mehta, 2015) In this regard, the absence of major risk factors predicts a much lower risk of ASCVD.(Stamler et al., 1999)

1.2.2 Established cardiovascular risk factors

Atherosclerosis is the underlying cause for ASCVD events.(Bergheanu, Bodde, & Jukema, 2017; Libby, Ridker, Hansson, & Leducq Transatlantic Network on, 2009) This insidious process begins with fatty streaks that are first seen in adolescence, which progress into plaques in early adulthood and culminate in thrombotic occlusions and CV events in middle age and later

life.(Bergheanu et al., 2017; Libby et al., 2009) A variety of factors, often acting in concert, are associated with an increased risk for atherosclerotic plaques in coronary arteries and other arterial beds.(National Cholesterol Education Program Expert Panel on Detection & Treatment of High Blood Cholesterol in, 2002) The classic CV risk factors which have been associated with CVD include gender, age, cholesterol, hypertension, DM and family history of premature CHD.(National Cholesterol Education Program Expert Panel on Detection & Treatment of High Blood Cholesterol in, 2002)

Gender and age

Age has been established as an independent CV risk factor. A cohort including 3.6 million individuals aged ≥40 years-old and screened for CVD demonstrated that the prevalence of CVD increased significantly with each decade of life.(Savji et al., 2013) The following rates of prevalent CVD were recorded: 2% in those aged 40-50 years old, 3.5% in 51-60 years old, 7.1% in 61-70 years old, 13% in 71-80 years old, 22.3% in 81-90 years old and 32.5% in 91-100 years old.(Savji et al., 2013)

Male sex has been long considered as a factor predisposing for CHD, although the potential mechanisms are not well understood. Several observational studies have demonstrated that the incidence and mortality related with CHD are higher in males.(D'Agostino et al., 2008; Kappert et al., 2012)

Family history of premature cardiovascular disease

Family history of CVD is a well-established CV risk factor, particularly among younger individuals.(Otaki et al., 2013; Sivapalaratnam et al., 2010) History of ASCVD or CVD death in a first-degree relative aged ≤55 years old for males and ≤65 years old for females is defined as positive family history of premature CVD.(Stone et al., 2014) However, it has been recently proposed that a less strict definition of premature CVD could include CVD in a first-degree relative of any age or other manifestations of atherosclerosis beyond myocardial infarction (MI) or CVD death, such as stroke or transient ischemic attack, CHD requiring revascularization in the absence of MI, PAD, and abdominal aortic aneurysm.(J. Patel et al., 2018) The importance of a family history of premature CVD death appears to be magnified in families with multiple

premature deaths.(Ranthe et al., 2012) The Danish Family Relations Database included 3,985,301 persons born from 1950 to 2008 and followed for nearly 90 million person-years.(Ranthe et al., 2012) This study demonstrated that persons derived from families with 2 or more premature CV deaths among first-degree relatives had a 3-fold greater risk of incident CVD before the age of 50 (incidence Relative Risk (RR): 3.30, 95% confidence intervals [95% CI]: 2.77-3.94).(Ranthe et al., 2012) Nevertheless, family history of CVD is not integrated in the available tools estimating CV risk.(Mach et al., 2020; Panagiotakos et al., 2007; Yancy et al., 2017) Rather, it is considered as a risk-enhancing factor by the most recent European and American lipid guidelines.(Grundy et al., 2019; Mach et al., 2020)

Hypertension

Hypertension has been long considered as an independent factor for CHD and stroke.(Lewington et al., 2002; Miura et al., 2001) A cohort including over 1.25 million subjects aged ≥30 years old without baseline CVD showed that those with hypertension experienced a higher CVD risk compared with those having normal blood pressure (BP) levels (63.3 vs. 46.1%).(Rapsomaniki et al., 2014)

Cholesterol

Evidence for the pathogenic role of serum cholesterol has largely come from randomized controlled trials (RCTs) showing that reductions in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels reduce coronary events and mortality in the setting of both primary and secondary prevention.(Amarenco et al., 2006; Downs et al., 1998; Ridker et al., 2008; Shepherd et al., 1995) The determination of which cholesterol levels are 'normal' has long been the subject of debate among professional societies.(Catapano et al., 2016; European Association for Cardiovascular et al., 2011; Mach et al., 2020; National Cholesterol Education Program Expert Panel on Detection & Treatment of High Blood Cholesterol in, 2002; Stone et al., 2014) TC and high-density lipoprotein cholesterol (HDL-C) levels are considered by the available tools for CV risk estimation.(Mach et al., 2020; Panagiotakos et al., 2007; Yancy et al., 2017)

Diabetes Mellitus

Insulin resistance, hyperinsulinemia and elevated blood glucose are associated with a 3-fold increase in CVD incidence.(Almdal, Scharling, Jensen, & Vestergaard, 2004; Yusuf et al., 2004) Traditionally, all-cause mortality risk associated with DM is thought to be similar to that of a prior MI,(Vaccaro et al., 2004) and DM has been considered as a CHD equivalent.(Mach et al., 2020) Nowadays, DM patients are categorized as very-high, high or medium risk depending on the presence of ASCVD, target organ damage or multiple risk factors and duration of the disease.(Cosentino et al., 2020) Diabetic patients have a greater burden of other atherogenic risk factors, such as hypertension, obesity, atherogenic dyslipidemia as well as elevated plasma fibrinogen and other thrombotic risk factors.(Cosentino et al., 2020; Mach et al., 2020) CVD risk in diabetics varies widely with the intensity of these risk factors and current guidelines suggest aggressive management and treatment.(Cosentino et al., 2020; Mach et al., 2020)

Smoking

Undoubtedly, cigarette smoking is an important CVD risk factor. Several cohorts have demonstrated that cigarette smoking dramatically increases the risk of incident MI up to 600%.(Njolstad, Arnesen, & Lund-Larsen, 1996; Prescott, Hippe, Schnohr, Hein, & Vestbo, 1998; Yusuf et al., 2004) An observational cohort study of 8,770 participants has recently shown that former heavy smoker CVD risk was significantly lower within 5 years of smoking cessation relative to current smokers (hazard ratio [HR]: 0.61).(Duncan et al., 2019) Nevertheless, CVD risk remained significantly elevated for at least 5 to 10 years and possibly for 25 years after cessation relative to never smokers.(Duncan et al., 2019)

1.2.3 Novel cardiovascular risk factors

Lipids and lipoproteins

Apart from LDL-C and HDL-C, the following lipid and lipoprotein abnormalities are associated with increased CHD risk: hypertriglyceridemia,(Rosenson, Davidson, Hirsh, Kathiresan, & Gaudet, 2014) increased non-high-density lipoprotein cholesterol (non-HDL-C),(Boekholdt et al., 2012) increased lipoprotein (a) (Lp(a)),(A. Bennet et al., 2008) increased apolipoprotein

(apo) C-III,(Jorgensen, Frikke-Schmidt, Nordestgaard, & Tybjaerg-Hansen, 2014) small-dense LDL particles (St-Pierre et al., 2001) and different genotypes of apoE.(A. M. Bennet et al., 2007) Available evidence suggests that triglyceride-rich lipoproteins (TRLs), marked by high triglycerides (TG), are strong and independent predictors of ASCVD-related and all-cause mortality, and that their cholesterol content (remnant cholesterol) are strong predictors of ASCVD.(Nordestgaard, 2016) Also, genetic studies using the Mendelian randomization design have demonstrated that TRLs are causally associated with ASCVD and all-cause mortality.(Nordestgaard, 2016)

LDL-C is a measure of cholesterol contained in the major atherogenic lipoprotein, whereas non-HDL-C represents the sum of the mass of cholesterol and cholesterol ester in all atherogenic lipoproteins (chylomicrons, very-low-density lipoprotein [VLDL] and their remnants, low-density lipoprotein (LDL) and Lp(a)) with apoB being their major apolipoprotein constituent.(Mach et al., 2020) Based on published epidemiological studies containing estimates of the relative risks of non-HDL-C and apoB for fatal or non-fatal ischemic cardiovascular events, a meta-analysis of 12 independent reports, including 233,455 subjects and 22,950 events, showed that apoB and non-HDL-C were more potent markers of CVD risk when compared with LDL-C.(Sniderman et al., 2011)

Lp(a) is an LDL particle with an apo(a) moiety covalently bound to its ApoB component.(Mach et al., 2020) It is <70 nm in diameter and can freely flux across the endothelial barrier, where it can become -similarly to LDL- retained within the arterial wall and thus increase the risk of ASCVD.(Mach et al., 2020) A recent Mendelian randomization study showed that the causal effect of Lp(a) on the risk of ASCVD is proportional to the absolute increase in plasma Lp(a) levels.(Burgess et al., 2018) Importantly, this study also suggested that people with extremely high Lp(a) levels >180 mg/dL (>430 nmol/L) may have an increased lifetime risk of ASCVD similar to that of people with heterozygous familial hypercholesterolemia (HeFH).(Burgess et al., 2018) Because about 90% of a person's Lp(a) level is inherited, extremely elevated Lp(a) represent an inherited lipid disorder that is associated with extremely high lifetime risk of ASCVD and is 2-fold more prevalent than HeFH.(Burgess et al., 2018)

ApoC-III is an atherogenic protein found on HDL, VLDL and LDL.(Wyler von Ballmoos, Haring, & Sacks, 2015) A meta-analysis of 11 studies including 2,832 cases with CV events showed significantly higher levels of apoC-III in the non-HDL fraction of plasma in CVD subjects compared with controls.(Wyler von Ballmoos et al., 2015) No difference was noticed for apoC-III levels in HDL and a trend toward higher total plasma apoC-III in those with CVD.(Wyler von Ballmoos et al., 2015)

LDL consists of several subclasses with distinct sizes, densities, and physicochemical compositions.(Hirayama & Miida, 2012) Accumulating evidence has shown that a predominance of small dense LDL is closely associated with CHD.(Hirayama & Miida, 2012) Small dense LDL-C concentrations are elevated in groups at a high risk for CHD, such as patients with type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS).(Hirayama & Miida, 2012)

ApoE gene, which affects the clearance of lipoproteins, has 3 major alleles: ε2, ε3, and ε4, coding for 3 isoforms: apoE2 (Cys112/Cys158), the most common apoE3 (Cys112/Arg158) and apoE4 (Arg112/Arg158).(El-Lebedy, Raslan, & Mohammed, 2016) ApoE isoforms have different effects on lipoprotein metabolism and certain polymorphisms (especially apoE4) have been associated with increased CVD risk.(El-Lebedy et al., 2016)

Chronic Kidney Disease

The increased CHD risk in patients with end-stage renal disease has been well-described.(Gansevoort et al., 2013) Mild to moderate renal dysfunction is also associated with a substantial increase in CHD risk.(Gansevoort et al., 2013) In this context, recent guidelines consider chronic kidney disease (CKD) of stage 3-4 (estimated Glomerular Filtration Rate [eGFR] <30 ml/min/1.73 m^2) as very high-risk status, whereas patients with eGFR 30-60 ml/min/1.73 m^2 are consider to be at high CV risk.(Mach et al., 2020)

Inflammatory markers

Strong evidence suggests that C-reactive protein,(Emerging Risk Factors et al., 2010) interleukin-6,(Collaboration et al., 2012) and myeloperoxidase (Karakas et al., 2012) are associated with increased CVD risk. Furthermore, CVD has also been associated with a variety

of other markers of inflammation, such as elevated levels of white blood cells, erythrocyte sedimentation rates, interleukin-18, tumor necrosis factor alpha, transforming growth factor beta, soluble intercellular adhesion molecule-1, P-selectin, cathepsin S and lipoprotein-associated phospholipase A2.(Agarwal et al., 2014; Danesh et al., 2004; Haim et al., 2002; Horne et al., 2005; Jobs et al., 2011; Oei et al., 2005; Pai et al., 2004; Ridker, Buring, & Rifai, 2001; Tiret et al., 2005; Valgimigli et al., 2005)

Metabolic syndrome

Patients with the constellation of abdominal obesity, hypertension, dysglycemia, and dyslipidemia are considered to have the co-called MetS.(Alberti et al., 2009) Such individuals have a 2-fold increased risk of CHD and all-cause mortality.(Gami et al., 2007)

1.2.4 Other cardiovascular risk factors

Several other factors, such as carotid artery intima-media thickness,(Bots et al., 2007) arterial stiffness (measured as the aortic pulse wave velocity between the carotid and femoral arteries),(Cooper et al., 2016) calcium deposits in extracoronary arteries, particularly in the aortic arch and abdominal aorta (Bos et al., 2015) and coronary artery calcification are prognostic markers of CVD.(P. G. Jorgensen et al., 2014) Likewise, resting electrocardiogram abnormalities, such as ST depression, T-wave inversion, left ventricular hypertrophy or strain, and premature ventricular contractions are associated with increased CVD risk.(P. G. Jorgensen et al., 2014) In addition, left ventricular hypertrophy,(Estes, Zhang, Li, Tereshchenko, & Soliman, 2015) endothelial dysfunction induced by dyslipidemia and oxidative stress,(Heitzer, Schlinzig, Krohn, Meinertz, & Munzel, 2001) along with resting and peak exercise heart rate are related with CVD and CV mortality.(Ho et al., 2014)

Moreover, other systemic conditions, such as androgen deficiency,(Ohlsson et al., 2011) premature menopause,(Muka et al., 2016) systemic autoimmune diseases, especially rheumatoid arthritis, psoriatic arthritis and systemic lupus erythematosus,(Manzi et al., 1997; Solomon et al., 2003) acute infectious illnesses,(Musher, Abers, & Corrales-Medina, 2019) non-alcoholic fatty liver disease,(Targher, Day, & Bonora, 2010) abnormal sleep or sleep apnea (St-

Onge et al., 2016) and small for gestational age (Hubinette et al., 2001) have been associated with increased incidence of CVD.

1.3 Familial hypercholesterolemia

1.3.1 Definition and prevalence of familial hypercholesterolemia

Familial hypercholesterolemia (FH) is the most common inherited metabolic disease caused by mutation of one of the genes involved in LDL-C catabolism and related with premature CHD.(Austin, Hutter, Zimmern, & Humphries, 2004b; F. Barkas, Liberopoulos, Liamis, & Elisaf, 2016; Vallejo-Vaz et al., 2015) The following three clinical definitions of FH represent the most commonly used: i) Simon Broome (Table 1), ii) Dutch Lipid Clinic Network (DLCN) (Table 2) and iii) American Heart Association (AHA) criteria for the clinical diagnosis of FH: LDL-C >190 mg/dL (>4.9 mmol/L) and either a first degree relative with LDL-C>190 mg/dL or with known CHD (55 years men; <60 years women).(Benn, Watts, Tybjaerg-Hansen, & Nordestgaard, 2016; Stone et al., 2014)

The prevalence varies on the definition used and population studied. Few patients in a clinical practice have been diagnosed with FH using a definition including genetic testing. Homozygous patients are rare and have an estimated prevalence of approximately 1:300,000 to 1:400,000.(Sjouke et al., 2015) The worldwide HeFH prevalence is estimated up to ~1/200-300 (Mach et al., 2020), whereas HeFH occurs in about 1 in 250 people in Greece.(Nordestgaard et al., 2013) In patients with ASCVD, the prevalence might be higher and reach 2-5%.(Nanchen et al., 2016) In patients with premature ASCVD, the prevalence is estimated to be 8-19%.(Pang et al., 2015) Although 7% of American adults have an untreated LDL-C ≥190 mg/dL, only 1.7% of those carry an FH mutation.(Khera et al., 2016)

Table 1 *Simon Broome criteria for the definition of familial hypercholesterolemia*

Criteria	Description
a	Total cholesterol >290 mg/dL (7.5 mmol/L) in adults or a total cholesterol >259 mg/dL (6.7 mmol/L) in children aged less than 16 years, or
	Low-density lipoprotein cholesterol >189 mg/dL (4.9 mmol/L) in adults or >155 mg/dL (4.0 mmol/L) in children
b	Tendinous xanthomata in the patient or a first-degree relative
c	DNA-based evidence of mutation in the *LDLR, PCSK9,* or *APOB* gene
d	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
e	Family history of raised total cholesterol >290 mg/dL (7.5 mmol/L) in a first- or second-degree relative
A "definite" FH diagnosis requires either criteria a and b, or criterion c. A "probable" FH diagnosis requires either criteria a and d, or criteria a and e.	

FH: familial hypercholesterolemia

Table 2 *Dutch Lipid Clinic Network criteria for the definition of familial hypercholesterolemia*

Criteria	Points
1) Family history	
• First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or • First-degree relative with known LDL-C above the 95th percentile	1
• First-degree relative with tendinous xanthomata and/or arcus cornealis, or • Children <18 years of age with LDL-C above the 95th percentile	2
2) Clinical history	
• Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
• Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1
3) Physical examination	
• Tendinous xanthomata	6
• Arcus cornealis before age 45 years	4
4) LDL-C levels	
▪ LDL-C ≥ 325 mg/dL (8.5 mmol/L)	8
▪ LDL-C 251 to 325 mg/dL (6.5-8.4 mmol/L)	5
▪ LDL-C 191 to 250 mg/dL (5-6.4 mmol/L)	3
▪ LDL-C 155 to 190 mg/dL (4-4.9 mmol/L)	1
5) DNA analysis	
▪ Functional mutation in the LDLR, apoB, or PCSK9 gene	8
A "definite" FH diagnosis requires >8 points A "probable" FH diagnosis requires 6 to 8 points A "possible" FH diagnosis requires 3 to 5 points	

FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein-cholesterol

1.3.2 Genetics in familial hypercholesterolemia

FH is caused mostly by functional mutations of one of three following genes: encoding LDL receptor (LDLR), gain-of-function mutations of the proprotein convertase subtilisin kexin 9 gene (PCSK9) and the apoB gene.(Austin et al., 2004b) Each of these three mutations impairs LDLR-mediated LDL catabolism resulting in markedly reduced hepatic capacity to clear LDLs from the circulation, with consequent LDL-C accumulation.(Austin et al., 2004b) Mutations in these three genes can be detected in ~80% of patients with definite FH and 20-30% of those with possible FH.(Austin et al., 2004b; Futema et al., 2013; Goldberg et al., 2011; Santos et al., 2016) Of those with one of these three mutations, 85-90% has LDLR mutations, 2-4% gain-of function PCSK9 mutations, and 1-12% apoB mutations.(Austin et al., 2004b; Futema et al., 2013; Goldberg et al., 2011; Santos et al., 2016) The majority of the rest patients with no causative single gene mutations probably have severe forms of polygenic hypercholesterolemia and a minority of those might have some as of yet undiscovered causative single gene mutations.(Fouchier et al., 2014; Santos et al., 2016)

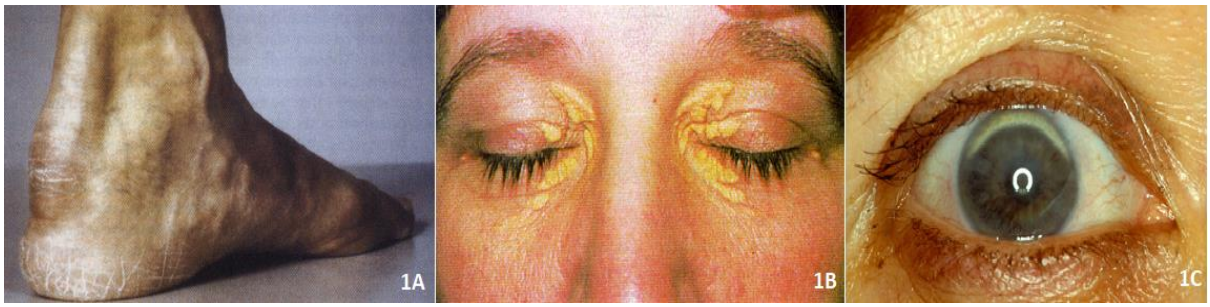
FH is an autosomal dominant disorder inherited with a gene dosing effect with the homozygotes being more adversely affected than heterozygotes.(Sjouke et al., 2015) Many patients, initially labeled as "homozygous FH" (HoFH) in clinical setting, are generally compound heterozygotes when parents are unrelated.(Sjouke et al., 2015) This is attributed to the very large number of distinct mutations in the gene encoding the LDL-R.(Sjouke et al., 2015) Therefore, it is more likely that someone would inherit two different mutations in the LDLR gene than the same one from unrelated parents.(Sjouke et al., 2015) True homozygosity can occur when a consanguinous union occurs between two heterozygotes or rarely in case that parents are not closely related.(Sjouke et al., 2015) However, a high prevalence of a limited number of LDLR mutations could happen in a regional population due to a founder gene effect.(Sjouke et al., 2015)

1.3.3 Clinical presentation of familial hypercholesterolemia

If left untreated, males and females with HeFH typically develop CHD before age 55 and 60, respectively, while HoFH individuals develop CHD very early in life and if they remain untreated, many will die before the age of 20.(Austin, Hutter, Zimmern, & Humphries, 2004a;

Hutter, Austin, & Humphries, 2004) FH should especially be considered in patients with CHD aged <55 years for men and <60 years for women, in those with relatives with premature CVD, tendon xanthomas or severely elevated LDL-C (adults >190 mg/dL [>4.9 mmol/L] or children >150 mg/dL [>3.9 mmol/L]), in case of sudden premature cardiac death in a family member and in first-degree relatives of patients with FH.(Mach et al., 2020)

In patients with suspected FH, the evaluation includes a complete history searching for clues indicating FH, such as personal and family history of premature ASCVD, tendon xanthomas, and elevated cholesterol levels (particularly if present during childhood).(Austin et al., 2004a; Hutter et al., 2004) Physical examination could reveal: i) tendon xanthomata, which are most common in the Achilles tendons and dorsum of the hands (Picture 1A), ii) planar xanthomas, which may occur on the palms of the hands and soles of the feet and are often painful, iii) xanthelasmas, cholesterol-filled, soft, yellow plaques that usually appear on the medial aspects of the eyelids (Picture 1B) and iv) corneal arcus, a white or grey ring around the cornea (Picture 1C).(Austin et al., 2004a; Hutter et al., 2004)



Picture 1 Findings of physical examination in patients with familial hypercholesterolemia
(A) Xanthoma (B) Xanthelasma (C) Corneal arcus

The characteristic fasting lipid profile in FH patients consists of elevated TC and LDL-C with normal or low HDL-C and normal TG levels.(Austin et al., 2004a; Hutter et al., 2004) Elevated TG levels do not exclude the diagnosis of FH, but other potential causes of hypertriglyceridemia should be considered (obesity, DM, or other mutations in triglyceride-regulating genes, in which case TG levels may also be elevated, such as familial combined hyperlipidemia).(Austin et al., 2004a; Hutter et al., 2004) A genetic testing for mutations in the LDLR, apoB, and PCSK9 genes may be offered to individuals with xanthomata and/or a clinical diagnosis of HoFH. On

the other hand, genetic testing in adults with a clinical picture consistent with heterozygous FH does not contribute substantially to clinical decision-making, and its role is not established. Genetic testing should be performed in consultation with a lipid specialist and/or geneticist.(Mach et al., 2020; Nordestgaard et al., 2013)

1.3.4 Diagnosis of familial hypercholesterolemia

The diagnosis of HeFH is made with genetic testing or clinical criteria. The confirmation of a causative mutation in LDL-R, apoB or PCSK9 genes secures this diagnosis. (Benn et al., 2016; Stone et al., 2014) When genetic testing is unavailable or considered unnecessary, DLCN and Simon Broome Register Group criteria are usually used for the diagnosis of HeFH (Tables 1 & 2).(Benn et al., 2016; Stone et al., 2014)

Criteria for the clinical diagnosis of HoFH include untreated LDL-C >500 mg/dL (>13 mmol/L) or treated LDL-C ≥300 mg/dL (>8 mmol/L) and i) cutaneous or tendon xanthoma before the age of 10 years or ii) elevated LDL-C levels consistent with HeFH in both parents.(Cuchel et al., 2014) Of note, untreated LDL-C levels <500 mg/dL do not exclude HoFH, particularly in young children.(Cuchel et al., 2014)

In case of FH identification in a patient, screening of all first-degree relatives is strongly recommended, including children beginning at the age two years.(Mach et al., 2020)

1.3.5 Prognosis of familial hypercholesterolemia

During the pre-statin era, the risk of premature CHD and stroke was very high in HeFH patients.(Austin et al., 2004a; Hutter et al., 2004) In a 1974 study of over 1,000 first and second degree relatives of 116 index patients, premature CHD risk was 52% for male and 32% for female relatives, whereas the corresponding rates were 13% and 9%, respectively.(Stone, Levy, Fredrickson, & Verter, 1974) At any level of untreated LDL-C, the prognosis for patients with HeFH is worse than the dyslipidemic individuals not fulfilling FH criteria.(Khera et al., 2016) A study of 1,386 patients with LDL-C ≥190 mg/dL in whom gene sequence was performed, patients with LDL-C ≥190 mg/dL and FH mutation had a 22-fold increased risk (odd ratio [OR]: 22.3, 95% CI: 10.7-53.2) for CAD, when compared with those having LDL-C <130 mg/dL.(Khera et al., 2016) HeFH patients who have sustained an acute coronary syndrome (ACS) and have

been treated with high-dose statins have a threefold mortality risk within one year than matched individuals without FH.(Nanchen et al., 2016) For homozygous patients, the extent of cholesterol achieved by any therapeutic intervention is a major determinant of survival.(Thompson et al., 2018)

1.3.6 Treatment of familial hypercholesterolemia

Intense LDL-C reduction in individuals with HeFH or HoFH decreases the progression of angiographically demonstrated CAD and reduces ASCVD events (myocardial infarction and stroke), CHD mortality, and all-cause mortality.(F. Barkas, Elisaf, & Milionis, 2015; Kane et al., 1990; A. Neil et al., 2008; Raal et al., 2011; Versmissen et al., 2008) The results of the observational cohorts evaluating the impact of therapy on mortality in FH patients are consistent with the findings of large statin RCTs enrolling individuals without FH.(Mills et al., 2008; Navarese et al., 2018)

Cholesterol-lowering treatment should be initiated as soon as possible after a diagnosis has been made.(Mach et al., 2020) The concept of cumulative cholesterol burden illustrates the importance of early treatment (Mach et al., 2020) Treatment should be initiated with high-intensity statin therapy (ie atorvastatin 40/80 mg or rosuvastatin 20/40 mg, which are capable of lowering LDL-C by 50-60%), usually in combination with ezetimibe (~20% further LDL-C reduction).(Mach et al., 2020)

The target of LDL-C ≥ 50% reduction from baseline and LDL-C <55 mg/dL (<1.4 mmol/L) are proposed in FH patients with prior ASCVD history or another major CV risk factor.(Mach et al., 2020) In the absence of ASCVD or another major risk factor, FH patients are categorized as high-risk, and the suggested LDL-C goals are a ≥50% LDL-C reduction from baseline and LDL-C <70 mg/dL (<1.8 mmol/L).(Mach et al., 2020)
Children can be treated with a statin from 8-10 years of age.(Mach et al., 2020) The proposed LDL-C target is <135 mg/dL (<3.5 mmol/L) at >10 years of age.(Mach et al., 2020)

Homozygous Familial Hypercholesterolemia

As the disease and its clinical consequences begin at birth, most patients will have been evaluated and treated in childhood.(Cuchel et al., 2014) By the time they are under the care of adult physicians, many will have established ASCVD.(Cuchel et al., 2014) However, a few will be fortunate enough to be disease free due to successful lipid-lowering treatment.(Cuchel et al., 2014) Homozygous FH patients often have untreated LDL-C of >500 mg/dL (>13 mmol/L).(Cuchel et al., 2014) The proposed LDL-C targets ranging from 55 to 135 mg/dL (1.4-3.5 mmol/L), as described above, may be difficult if not impossible to achieve even with the available lipid-lowering therapies.(Cuchel et al., 2014)

The patients should be treated with intensive LDL-lowering drug therapy (statins + ezetimibe) and, when available, with lipoprotein apheresis.(Cuchel et al., 2014) This treatment (every 12 weeks) can decrease plasma LDL-C levels by 55-70%.(Cuchel et al., 2014) The procedure frequency may be adjusted for each patient since lipid levels, symptoms, and other disease-related parameters change.(Cuchel et al., 2014) Maximally tolerated pharmacological therapy must be maintained.(Cuchel et al., 2014) Novel lipid-lowering therapies, such as lomitapide (inhibitor of microsomal triglyceride transfer protein) and mipomersen (mRNA inhibitor of apoB) have been approved by the Food and Drug Administration (FDA) as adjunct therapy for HoFH in patients aged ≥18 and ≥12 years, respectively; the former has also been approved by the European Medicines Agency.(Cuchel et al., 2014) PCSK9 inhibitors could be an additional therapeutic option in subjects with LDLR defective mutations or PCSK9 gain-of-function mutations, whereas inhibitors of cholesteryl ester transfer protein (CETP) in combination with statin could be effective in LDL-C and Lp(a) reduction in HoFH patients.(Cuchel et al., 2014) Finally, surgical approaches, such as liver transplantation or portocaval shunt, are available but rarely used nowadays.(Cuchel et al., 2014)

Heterozygous familial hypercholesterolemia

The vast majority of adult FH patients encountered in clinical practice will be heterozygotes and will usually have an untreated LDL-C ≥190 mg/dL.(Mach et al., 2020) Intensive lipid lowering therapy (high-intensity statins + ezetimibe) is recommended for all patients with HeFH.(Mach

et al., 2020) In case of not optimal LDL-C levels, PCSK9 inhibitors are additional proposed in HeFH individuals taking maximally tolerated lipid-lowering therapy or those not tolerating statins.(Mach et al., 2020) Investigational and novel medical therapies, such as mipomersen, CETP inhibitors and bempedoic acid have been used in patients with HeFH.(Raal, Hovingh, & Catapano, 2018) In patients who still remain above LDL-C target, historical options for additional intervention have included ileal bypass surgery, portacaval anastomosis and liver transplantation, but these interventions are rarely used in a HeFH patients.(Mach et al., 2020) Similarly, lipoprotein apheresis is also uncommonly used in such patients.(Mach et al., 2020)

1.4 Diet and cardiovascular disease

It has been estimated that more than half of deaths and disability from CHD and stroke could be prevented by modifications to lifestyle, such as diet, activity and smoking.(Iqbal et al., 2008) Despite the lower CVD mortality rates and the increased prescription of CV therapies during the last decade, the prevalence of CV risk factors, such as obesity, dyslipidemia and DM are dramatically increasing.(Timmis et al., 2018) In this context, all current guidelines agree that when treating people with elevated risk of CVD, the physicians should also emphasize on the management of lifestyle factors, such as i) smoking cessation, ii) increased physical activity, iii) management of BP, iv) management of lipids, v) management of DM, vi) healthy food choices and vii) weight management along with limiting central obesity.(American Heart Association Nutrition et al., 2006)

The dietary management of these CV risk factors include the manipulation of calorie balance, macronutrients (carbohydrates, proteins, fat), dietary fiber, micronutrients (salt), types of food (fruit, vegetables, nuts) and beverages (alcohol, sweeten beverages, coffee). Dietary interventions, such as low-fat and low-cholesterol diet, along with Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets have been evaluated in CV prevention and lipid management.(American Heart Association Nutrition et al., 2006)

1.4.1 Caloric balance

Maintaining caloric balance over time is important to maintaining healthy weight. Overnutrition leading to overweight and obesity is associated with premature mortality, CVD incidence, DM, hypertension, cancer and other diseases.(Adams et al., 2006; Renehan, Tyson, Egger, Heller, & Zwahlen, 2008; Willett, Dietz, & Colditz, 1999) In order to achieve calorie balance, the individuals should limit their typical calorie consumption, while also engaging in physical activity.(Adams et al., 2006; Renehan et al., 2008; Willett et al., 1999) Calculating total energy expenditure for recommended daily caloric intake is based on age, sex, weight, and activity level, whereas calculating one's actual daily caloric intake can be aided by using 24-hour dietary recall, a food diary or other assessment tools.(Adams et al., 2006; Renehan et al., 2008; Willett et al., 1999)

1.4.2 Carbohydrates

Classification of carbohydrates

Based on the number of sugar molecules in their chemical structures, carbohydrates are traditionally classified as simple starches (sugars, ie. mono- and disaccharides) or complex starches, (ie. polysaccharides). Considering the fact that complex carbohydrates cause smaller rises in blood glucose than simple carbohydrates, dietary guidelines recommend the use of complex rather than simple carbohydrates to control blood glucose levels in patients with DM.(Bantle et al., 2008) An additional classification of carbohydrates is based on their glycemic index (GI), which is a measure of the relative impact of carbohydrate-containing foods on serum glucose.(D. J. Jenkins et al., 1981) More specifically, a particular food's GI is determined by evaluating the incremental rises of blood glucose after the ingestion of a food containing 50 g carbohydrates compared with the same amount of carbohydrate from a reference food, such as white bread or glucose.(D. J. Jenkins et al., 1981) The following values are generally applied for GI definition of a particular food (using glucose as a reference): i) low GI (≤55), ii) medium GI (56-69) and iii) high GI (≥70).(D. J. Jenkins et al., 1981) Table 3 shows a few examples of GI in certain foods. Considering the fact that GI does not capture the entire glucose-raising potential of dietary carbohydrates, since the blood glucose response is not influenced only by the type, but also by the quantity of the consumed carbohydrate, the concept of glycemic load (GL) has

been additionally introduced.(Salmeron et al., 1997) Defined as the product of the GI value of a food and its carbohydrate content, GL incorporates both the quality and quantity of carbohydrate consumed and the interaction between them.(Englyst, Liu, & Englyst, 2007) In general, carbohydrate-rich foods with low fiber content have high GI and GL values (ie. potatoes, refined cereal products and many sugar-sweetened beverages).(Englyst et al., 2007) On the contrary, intact whole grains, legumes, fruits and vegetables with high fiber content provide low to very low GLs per serving.(Englyst et al., 2007) The following values are generally applied for defining the GL of a particular food per serving, using glucose as a reference: i) low GL (≤10), ii) medium GL (11-19) and iii) high GL (≥20). The definition of daily GL includes: i) low GL (≤80) and ii) high GL (≥120).(Englyst et al., 2007) Finally, carbohydrates from grains may also be classified by whether the grain is whole or has been refined by removing all or part of the bran and germ.(J. M. Jones, Garcia, & Braun, 2019) Products are allowed to be marketed as whole grain if they are at least 51% whole grain.(J. M. Jones et al., 2019) The majority of the fiber, vitamins, minerals, and phytochemicals reside in the bran and germ fractions, and most of these are removed with refining.(J. M. Jones et al., 2019) The evidence for health benefits of dietary fiber is based on consumption of fiber in food and not the purified fiber that lacks all of these potentially beneficial components that accompany the fiber.(J. M. Jones et al., 2019)

Carbohydrates should make up 45-65% of total caloric intake, as recommended by the United States Dietary Guidelines.(USDA, 2015)

Table 3 *Glycemic index for certain foods (Atkinson, Foster-Powell, & Brand-Miller, 2008)*

Food	Glycemic index (glucose = 100)	Food	Glycemic index (glucose = 100)
HIGH-CARBOHYDRATE FOODS		**FRUIT AND FRUIT PRODUCTS**	
White wheat bread	75 ± 2	**Apple, raw**	36 ± 2
Whole wheat/whole meal bread	74 ± 2	**Orange, raw**	43 ± 3
Specialty grain bread	53 ± 2	**Banana, raw**	51 ± 3
Unleavened wheat bread	70 ± 5	**Pineapple, raw**	59 ± 8
Corn tortilla	46 ± 4	**Mango, raw**	51 ± 5
White rice, boiled	73 ± 4	**Watermelon, raw**	76 ± 4
Brown rice, boiled	68 ± 4	**Strawberry jam/jelly**	49 ± 3
Sweet corn	52 ± 5	**Apple juice**	41 ± 2
Spaghetti, white	49 ± 2	**Orange juice**	50 ± 2
Spaghetti, whole meal	48 ± 5		
Rice noodles	53 ± 7	**VEGETABLES**	
		Potato, boiled	78 ± 4
BREAKFAST CEREALS		**Potato, instant mash**	87 ± 3
Cornflakes	81 ± 6	**Potato, french fries**	63 ± 5
Wheat flake biscuits	69 ± 2	**Carrots, boiled**	39 ± 4
Porridge, rolled oats	55 ± 2		
Instant oat porridge	79 ± 3	**DAIRY PRODUCTS AND ALTERNATIVES**	
Rice porridge/congee	78 ± 9	**Milk, full fat**	39 ± 3
Millet porridge	67 ± 5	**Milk, skim**	37 ± 4
Muesli	57 ± 2	**Ice cream**	51 ± 3
Cornflakes	81 ± 6	**Yogurt, fruit**	41 ± 2
Wheat flake biscuits	69 ± 2	**Soy milk**	34 ± 4
		Rice milk	86 ± 7
Data are means ± Standard error of the mean			

Carbohydrates and cardiovascular disease

Large epidemiologic studies have demonstrated that higher intake of dietary and cereal fiber, along with whole grains are associated with lower CHD risk.(Reynolds et al., 2019)

Prospective cohort studies evaluating the effects of GI and GL on CVD risk are fewer than those evaluating DM risk, but in general they show that dietary GI and GL are associated with CHD risk.(Barclay et al., 2008; Halton et al., 2006; Liu et al., 2000; Shikany et al., 2010). A meta-analysis of 10 prospective studies (n=240,936) showed that the highest GI and GL quartiles were associated with a higher CHD risk in women by 26% and 55%, respectively, when compared with the lowest ones.(Mirrahimi et al., 2012). However, these findings were not confirmed by another meta-analysis.(Reynolds et al., 2019)

Nurses' Health Study (n=75,521) showed that GL-associated CHD risk was present after 20 years of follow-up (RR: 1.90, 95% CI: 1.15-3.15) and most evident among the obese subjects.(Halton et al., 2006) An additional analysis found no association between stroke and either GI or GL.(Oh et al., 2005) Nevertheless, a positive association between total carbohydrate intake and risk of hemorrhagic stroke was noticed (RR: 2.05, 95% CI: 1.10-3.83), mostly in the heavier women.(Oh et al., 2005) Finally, consumption of cereal fiber was associated with a lower risk of total and hemorrhagic stroke (RR: 0.66, 95% CI: 0.52-0.83 and RR: 0.51, 95% CI: 0.33-0.78, respectively).(Oh et al., 2005)

A few, but not all, short-term trials have demonstrated that low GI/GL diets have beneficial effects on CV risk factors.(Bouche et al., 2002; Dumesnil et al., 2001; Sacks et al., 2014) A meta-analysis of 28 RCTs comparing low- with high-GI diets over at least 4 weeks (n=1,272) showed that low-GI diets reduced TC (-0.13 mmol/L, 95%CI: -0.22 to -0.04, p=0.004) and LDL-C (-0.16 mmol/L, 95% CI: -0.24 to -0.08, p <0.0001) independently of weight loss, while no effects on HDL-C and TG were observed.(Goff, Cowland, Hooper, & Frost, 2013) On the other hand, a randomized, cross-over-controlled trial evaluating the effects of different GI diets on CV risk factors in 163 overweight individuals demonstrated that diets with low compared with high GI did not result in improvements in insulin sensitivity, lipid levels or systolic BP.(Sacks et al., 2014).

Mediterranean diet with low GL has been associated with a decrease in atherogenic lipoproteins, oxidized LDL, apoB and a beneficial effect on components of MetS, such as waist circumference, systolic and diastolic BP and TG.(J. L. Jones et al., 2012; J. L. Jones et al., 2011)

Although the observational data supports an association between GI and GL and CHD, there are no direct data derived from RCTs showing whether manipulation of dietary GI or GL will prevent or delay CHD development.

1.4.3 Fiber

Dietary fiber is the portion of plants that cannot be digested by enzymes in the gastrointestinal tract and its recommended amount is 14 g per 1000 calories, which translates to approximately 25 g to 36 g per day.(USDA, 2015) As shown in Table 4, fiber is available in a large variety of natural foods and supplements.

High fiber intake has been associated with a 24-38% reduction in CHD and stroke risk compared with low fiber intake and this benefit seems greater in case of fiber derived from grain rather than from fruit or other sources.(Ascherio et al., 1998; Jensen et al., 2004; Pietinen et al., 1996; Wolk et al., 1999). Moreover, there seems to be a dose response relationship, with increasing amounts of fiber intake associated with greater reduction in CVD risk. According to a pooled analysis of 10 prospective cohort studies (n=330,000), each 10 g per day increment in fiber intake was associated with a 14% reduction in CHD risk and 27% reduction in CV mortality.(Pereira et al., 2004) Similarly, the CV benefit of dietary fiber has been noticed in patients with established CVD. A prospective cohort study enrolling 4,000 patients diagnosed with a first-ever MI demonstrated that post-MI adherence to high-fiber diet was associated with lower CV (RR: 0.72, 95% CI: 0.52-0.99) and all-cause (RR: 0.73, 95% CI: 0.58-0.91) mortality.(S. Li et al., 2014)

The cardioprotective effect of high-fiber diets could be attributed to the induced reduction of insulin and BP levels and improvement of lipids.(Hartley, May, Loveman, Colquitt, & Rees, 2016; Ludwig et al., 1999) Indeed, a meta-analysis of 23 RCTs (n=1,513) examining the effect of dietary fiber showed a beneficial effect of increased fiber on TC (-0.23 mmol/L, 95% CI: -0.40 to -0.06), LDL-C (-0.14 mmol/L, 95% CI: -0.22 to -0.06) and diastolic BP (-1.77 mmHg, 95% CI: -2.61 to -0.92).(Hartley et al., 2016)

Table 4 *Amount of fiber in different types of food*

Food	Serving	Grams of fiber
Fruits		
Apple (with skin)	1 medium apple	4.4
Banana	1 medium banana	3.1
Oranges	1 orange	3.1
Prunes	1 cup, pitted	12.4
Juices		
Orange	1 cup	0.7
Vegetables		
Cooked		
Green beans	1 cup	4.0
Carrots	1/2 cup sliced	2.3
Peas	1 cup	8.8
Potato (baked, with skin)	1 medium potato	3.8
Raw		
Cucumber (with peel)	1 cucumber	1.5
Lettuce	1 cup shredded	0.5
Tomato	1 medium tomato	1.5
Spinach	1 cup	0.7
Legumes		
Baked beans, canned, no salt added	1 cup	13.9
Kidney beans, canned	1 cup	13.6
Lima beans, canned	1 cup	11.6
Lentils, boiled	1 cup	15.6
Breads, pastas, flours		
White bread	1 slice	0.6
Whole-wheat bread	1 slice	1.9
Pasta and rice, cooked		
Rice, brown	1 cup	3.5
Rice, white	1 cup	0.6
Spaghetti (regular)	1 cup	2.5
Nuts		
Almonds	1/2 cup	8.7
Peanuts	1/2 cup	7.9

Data from: USDA Food Data Central. Available at: https://fdc.nal.usda.gov (Accessed on April 18, 2020)

1.4.4 Fats

It has been long proposed that fat should make up 20-35% of total caloric intake.(USDA, 2015) However, recent evidence supports that lowering total fat intake has no meaningful effects on CHD, stroke, cancer, DM and long-term weight control.(Harcombe, Baker, DiNicolantonio, Grace, & Davies, 2016) This might be attributed to the fact that total dietary fat includes different fatty acids and food sources with divergent effects on health and current guidelines emphasize more on type of fats rather than total fat intake.(USDA, 2015)

Total fat intake

Populations consuming a higher total fat intake do not always develop CHD. For instance, in the Seven Countries Study, the lowest CHD incidence was noticed in Crete and Japan.(Keys et al., 1986) Similarly, other cohorts revealed no association of total fat intake with either CHD or CV mortality.(Skeaff & Miller, 2009) Women's Health Initiative, the largest RCT evaluating the effect of changing diet upon CV outcomes, randomly assigned 48,835 women (97% with no history of CVD) to an intensive behavior-modification group, aiming to reduce total fat intake to 20% and increase daily intake of vegetables and grains or to a control group who received dietary education materials.(Howard et al., 2006) After six years, women in the intervention group had decreased total fat intake compared with the control group (28.8 vs 37% of calories from fat), but the intervention had no effect on overall CHD (HR: 0.94, 95% CI: 0.86-1.02) or stroke (HR: 1.02, 95% CI: 0.90-1.17).(Howard et al., 2006) Although the intervention group reduced the potentially harmful saturated and trans fats, they also reduced the potentially beneficial monounsaturated (MUFAs) and polyunsaturated fats (PUFAs), while increasing refined carbohydrates.(C. A. Anderson & Appel, 2006)

Trans fatty acids

As shown in Table 5, the quality of consumed fat and its sources appear to be considerably more important for health than total fat intake. Low levels of trans fatty acids occur naturally in some foods, especially dairy and meats from ruminants (cows, sheep and goats). (Chowdhury et al., 2014; Mozaffarian, Katan, Ascherio, Stampfer, & Willett, 2006) However, much higher levels of

trans fatty acid consumption derive from the industrial partial hydrogenation of unsaturated fatty acids and confer to harmful CV effects.(Chowdhury et al., 2014; Mozaffarian et al., 2006)

Table 5 *Sources and main effects of dietary fat*

Type of fat	Chief food sources	Leading food contributors in diets of adults in the United States	Effects on cholesterol	Effects on coronary heart disease
Trans fatty acids, from partially hydrogenated vegetable oils	Stick and full-fat margarine, commercial baked goods, deep-fried foods	Fast food, margarines, commercial baked goods (sweet rolls, cookies, donuts)	Increases low-density lipoprotein cholesterol, lowers high-density lipoprotein cholesterol	Increases risk of coronary heart disease
Saturated fatty acids	Dairy foods, red meat, some plant oils (coconut, palm)	Dairy foods, especially cheese, milk, ice cream, red meat	Increases total cholesterol	May increase risk of coronary heart disease
Monounsaturated fatty acids	Vegetable sources (canola, olive oil), also from meat, dairy	Beef, margarines, chicken, olive oil	Lowers low-density lipoprotein cholesterol and triglycerides, maintains high-density lipoprotein cholesterol	Probably has no association
Polyunsaturated fatty acids; n-6	Safflower, sunflower, and corn oils	Mayonnaise, margarines, salad dressing, nuts, chicken, peanut butter	Lowers low-density lipoprotein cholesterol and triglycerides, increases high-density lipoprotein cholesterol	May reduce risk of coronary heart disease
Polyunsaturated fatty acids; n-3	Canola, soybean, flaxseed, walnut oil, wheat germ, vegetables of cabbage family For longer-chain n-3 fatty acids: seafood, especially fatty fish	Alpha-linolenic acid (18:3): mayonnaise, salad dressing, margarines, beef longer-chain n-3: tuna, other dark fish, shrimp	Lowers low-density lipoprotein cholesterol and triglycerides, maintains high-density lipoprotein cholesterol	May reduce risk of coronary heart disease

High intake of trans fatty acids has been associated with increased LDL-C, TC/HDL-C, apoB/apoA-I, Lp(a) and lower HDL-C concentrations.(Mozaffarian & Clarke, 2009; Mozaffarian et al., 2006) Several observational studies have linked the consumption of trans fatty acids with adverse CV outcomes.(Guasch-Ferre et al., 2015; Hu et al., 1997; D. D. Wang et al., 2016) In an analysis from the Nurses' Health Study, each 2% increase in energy from trans fatty acids doubled CHD risk (RR: 1.93, 95% CI: 1.43-2.61).(Hu et al., 1997) It has also been suggested that replacement of trans fatty acids with other sources of fat, even saturated fatty acids, can reduce CHD risk.(Guasch-Ferre et al., 2015; D. D. Wang et al., 2016)

In contrast to the trans fatty acids discussed above, trans-palmitoleic acid, a trans fatty acid derived from natural foods, has not been associated with increased CV risk (Mozaffarian et al., 2006)

Saturated fatty acids

While recommendations on saturated fat have conventionally grouped all saturated fatty acids together, increasing evidence indicates that different saturated fatty acids along with their different food sources have divergent effects on CV health.(Mensink, Zock, Kester, & Katan, 2003) For instance, saturated fatty acids with carbon chain lengths of 14 (myristic) and 16 (palmitic), mainly found in dairy products and red meats, increase both LDL-C and HDL-C, decrease TRLs, but has no effect on TC/HDL-C.(Mensink et al., 2003) On the other hand, stearic acid (18 carbons), another component of beef and the main fatty acid of cocoa butter, has smaller effects on LDL-C and HDL-C, but significantly lowers TC/HDL-C.(Mensink et al., 2003) Systematic reviews and meta-analyses of prospective observational studies and RCTs have found no association between the overall intake of total saturated fat and CHD risk.(Chowdhury et al., 2014; Hooper, Martin, Abdelhamid, & Davey Smith, 2015; Siri-Tarino, Sun, Hu, & Krauss, 2010) Very low saturated fat intake of saturated fat, such as levels <7% in some Asian countries, has been associated with a higher risk of stroke, especially hemorrhagic.(Dehghan et al., 2017) Although causality of these associations has not been established yet, hypothesized mechanisms include increased cerebral vascular fragility from low intakes of saturated fat and/or animal protein.(Dehghan et al., 2017)

Medium-chain triglycerides (including saturated fats with carbon lengths at or below 12 carbons) have been thought to be metabolically protective, while very long-chain saturated fats (lengths of 20, 22, or 24 carbons) have been linked to lower CHD and heart failure risk.(Lemaitre et al., 2015; Lemaitre et al., 2014)

Despite the conflicting data on the association between saturated fat intake and CVD, current guidelines maintain the decades-old recommendation to keep total saturated fat consumption below 10%.(USDA, 2015)

Monounsaturated fatty acids

In contrast to saturated fatty acids, nearly all (>90%) monounsaturated fat in foods is oleic acid, an 18-carbon fatty acid with a single double bond.(USDA, 2015) As shown in Table 5, MUFAs mainly come from red meats and dairy fats (each containing about equal amounts of saturated fat and monounsaturated fat) and a smaller amount coming from plant oils like nuts, avocadoes, and olive oil which is greatly consumed in Mediterranean countries. (USDA, 2015)

Meta-analyses of prospective observational studies and RCTs have found no association between MUFAS intake and CHD risk (Chowdhury et al., 2014; Mozaffarian & Clarke, 2009) Only a meta-analysis identified a protective role of MUFAs against CVD, but it was limited to olive oil studies, rather than studies of combined, animal or other sources of monounsaturated fat.(Schwingshackl & Hoffmann, 2014)

The replacement of saturated fats with MUFAs may decrease LDL-C, TG and maintain HDL-C (Mata, Alvarez-Sala, Rubio, Nuno, & De Oya, 1992; Mensink & Katan, 1992), whereas they can also decrease LDL-C oxidation.(Reaven et al., 1993) On the other hand, replacing carbohydrates with either MUFAs or PUFAs improved several markers of glycemia.(Imamura et al., 2016)

In cross-cultural studies, Mediterranean populations that consume high amounts of MUFAs from extra-virgin olive and nuts appear to be protected against CVD.(Keys et al., 1986) A RCT including 7,447 individuals at high CV risk demonstrated that extra virgin olive oil and mixed nuts combined with a traditional Mediterranean-type diet reduced by ~30% the risk of the primary composite outcome (heart attack, stroke, and death)(Estruch et al., 2018) Therefore,

evidence supports consuming plant foods rich in MUFAs, in particular extra virgin olive oil and tree nuts, rather than trying to increase MUFAs consumption from all sources.

Polyunsaturated fatty acids

PUFAs are classified into 2 groups: the n-6 family PUFAs (eg, linoleic acid, arachidonic acid) and the n-3 family PUFAs (ie, alpha-linolenic acid, eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]).(USDA, 2015) In contrast to saturated and monounsaturated fats which are readily synthesized in the liver from either dietary starch or sugars, the parent (18-carbon) fatty acids of both n-6 family (linoleic acid) and n-3 family of PUFAs (alpha-linolenic acid) cannot be synthesized and are therefore essential nutrients for humans.(USDA, 2015) As shown in Table 5 and 6, dietary n-3 fatty acids derive from the plants (alpha linolenic acid, eg, from walnuts, canola, soybean) or fish/shellfish.(USDA, 2015) EPA and DHA are present in all fish and shellfish, but especially dark meat or oily fish). (USDA, 2015)

N-6 fatty acids

In contrast to saturated fats, plant-derived n-6 fatty acids (ie. from soybean, safflower, sunflower, corn oils) lower both lower serum LDL-C, TG and TC/HDL-C ratio and increase HDL-C.(Mensink & Katan, 1992)

Consistent with the beneficial effect on lipids, both estimated dietary consumption or blood biomarkers of total n-6 PUFAs and linoleic acid have been associated with lower CHD risk. A meta-analysis including 310,062 individuals without previous CVD showed that the highest PUFAs intake was associated with a 15% lower CHD risk (RR: 0.85; 95% CI: 0.78-0.92) and a 21% lower CHD-related mortality risk (RR: 0.79; 95% CI: 0.71-0.89), when compared with the lowest intake.(Farvid et al., 2014) Similarly, replacing butter and other animal fats with n-6-rich oils (predominantly soybean oil) lowered CHD incidence and mortality.(Farvid et al., 2014)

N-3 fatty acids

The n-3 family of PUFAs includes EPA and DHA, which are found in fish oil, especially cold-water oily fish such as salmon, anchovies, mackerel, herring, sardines and tuna (Table 6). The third member of the family is alpha-linoleic acid found in the oil of plants, such as walnuts, soybeans and canola.(USDA, 2015)

A plethora of studies has demonstrated that fish oil n-3 fatty acids have TG-lowering, BP-lowering, antiarrhythmic, antithrombotic and anti-inflammatory effects.(Sokola-Wysoczanska et al., 2018) Regarding their impact on lipids, fish oil consumption can lower serum TG concentrations by 25-30% by lowering VLDL production or enhancing the clearance of TG-chylomicrons.(Oscarsson & Hurt-Camejo, 2017) The dose-response appears to be fairly linear; dietary doses or low-dose EPA and DHA (<1 g/day) supplementation lead to lower TG reduction, whereas higher doses (3 to 4 g/day) appreciably lower TG levels.(Brinton et al., 2018)

Table 6 *Fish sources of n-3 fatty acids*

Fish sources of n-3 fatty acids	
Mackerel – frozen or fresh	Very high source
Kippers – fresh, frozen or canned	
Pilchards – fresh or frozen	
Tuna or trout – fresh or frozen	
Sprats – fresh or frozen	
Mackerel – smoked or canned	
Sardines – fresh or frozen	
Herring – pickled, fresh or frozen	
Sild or skippers – canned	
Salmon – canned in brine or smoked	
Crab – fresh	
Herring – canned	
Trout – smoked	
Swordfish (only eat once a week)	
Salmon fish cakes	
Salmon fish paté	
Tuna – canned in oil	
Crab – canned brine	
Eel – fresh or jellied	
Fish pâté – crab, salmon, sardines	
Cod or haddock – fresh or frozen	
Fish cakes or fish fingers (white)	
Tuna – canned in brine or water	Low source

High sources per average serving are above the dashed line

Two meta-analyses of large cohorts (n=220,000) with long follow-ups (~12 years) demonstrated that higher fish consumption was associated with a lower risk of fatal CHD by 15-17%.(K. He et al., 2004; Whelton, He, Whelton, & Muntner, 2004) He et al. observed a dose–response relationship between fish consumption and fatal CHD, since individuals who consumed fish five or more times per week had a 38% lower risk of fatal CHD (RR: 0.62, 95% CI: 0.46-0.82).(K. He et al., 2004) On the other hand, evidence for an inverse association between fish consumption and non-fatal MI was weak, even though there was a significant association for those eating fish five times per week or more.(K. He et al., 2004)

The evidence for cardiovascular benefits of plant-derived alpha-linolenic acid remains uncertain. A meta-analysis of 27 observational studies demonstrated that the highest quartile of dietary intake of alpha-linolenic acid was associated with a lower CVD risk by 10%, when compared with the lowest one (13 studies, RR: 0.90, 95% CI: 0.81-0.99).(Pan et al., 2012)
Several meta-analyses of RCTs have demonstrated conflicting results regarding the impact of n-3 fatty acids on CVD.(Hooper et al., 2006; Leon et al., 2008; Marik & Varon, 2009; Rizos, Ntzani, Bika, Kostapanos, & Elisaf, 2012; Schwab et al., 2014; Zhao et al., 2009) It has to be noticed that the majority of those included trials investigating the effect of omega-3 fatty acids in fish oils, but also those administering a fish advice or margarines enriched with alpha-linoleic acid.(Hooper et al., 2006; Leon et al., 2008; Marik & Varon, 2009; Rizos et al., 2012; Schwab et al., 2014; Zhao et al., 2009) Nevertheless, a recent meta-analysis including 79 RCTs (n=112,059) suggested no effect of increased consumption of either fish- or plant-derived omega-3 fatty acids on total mortality and CVD incidence.(Abdelhamid et al., 2018) There was a suggestion that fish-oil fatty acids reduced CHD events (RR: 0.93, 95%: CI 0.88 to 0.97), but this was not maintained in sensitivity analyses.(Abdelhamid et al., 2018)

On the other hand, 2 recently published RCTs have demonstrated a beneficiary effect of omega-3 fatty acids on CV outcomes in high-risk individuals. In the ASCEND trial (A Study of Cardiovascular Events in Diabetes), CV mortality risk was significantly reduced by 19% with 840 mg/d of EPA/DHA in 15,480 diabetic individuals without previous CVD.(Bowman et al., 2018) However, the primary composite end points were not significantly reduced.(Bowman et al., 2018) Similarly, REDUCE-IT (the Reduction of Cardiovascular Events with Icosapent Ethyl–

Intervention Trial) demonstrated a 25% decrease in the primary CV end point with 4 g/d EPA in 8,179 statin-treated patients with elevated TG and at high CV risk (135–499 mg/dL).(Bhatt et al., 2019) The rates of additional ischemic end points were significantly lower in the EPA group than in the placebo group, including the rate of CV death (HR: 0.80; 95% CI: 0.66-0.98).(Bhatt et al., 2019)

Considering the above evidence, FDA advises general population not to exceed 3 g/day of EPA/DHA and with up to 2 g/day from dietary supplements without the guidance of a clinician.(USDA, 2015)

Cholesterol

Dietary cholesterol raises TC but is a less important contributor than saturated fat.(Hegsted, Ausman, Johnson, & Dallal, 1993) Eggs are a chief source of dietary cholesterol, but the association between regular egg consumption and risk of CHD and stroke remains uncertain. In a meta-analysis of 8 prospective cohort studies (n~474,000 participants), there was no association between egg consumption and CHD or stroke risk (RR: 0.99, 95% CI: 0.85-1.15 and RR: 0.91, 95% CI:0.81-1.02, for each additional daily egg, respectively).(Rong et al., 2013)

For most individuals, only a minor emphasis on reducing dietary cholesterol alone is given, since it does not contribute so much to serum cholesterol and CV endpoints than saturated or trans fatty acids.(Mozaffarian & Ludwig, 2015; USDA, 2015) However, some patients either consuming very large amounts of dietary cholesterol or whose serum LDL-C response to moderate cholesterol intake is unfavorable may benefit from a reduction in cholesterol intake.(USDA, 2015)

1.4.5 Protein

Protein should make up 10-35% of total caloric intake, as recommended by the United States Dietary Guidelines.(USDA, 2015) Individuals should be counseled to eat a variety of healthy protein-rich foods, including fish, lean meat, poultry, eggs, beans, peas, soy products, unsalted nuts and seeds, whereas they should avoid protein sources with unhealthy fats.(USDA, 2015) Common sources of dietary protein include whole foods (eg, meat, fish, egg, vegetables, milk)

and protein powders (eg, casein, whey, soy).(USDA, 2015) The source of protein has a differential effect on health. For instance, as it will be discussed below, red meats are associated with modestly increased mortality compared with white meats.

1.4.6 Salt

Undoubtedly, salt restriction leads to important falls in BP in both hypertensive and normotensive individuals, irrespective of sex and ethnic group.(F. J. He, Li, & Macgregor, 2013) This beneficiary effect could lead to the reduction of CVD incidence. Indeed, a meta-analysis of 13 prospective cohorts with 177,025 participants followed-up for 3.5-19 years demonstrated that higher salt intake increased the risk of stroke (RR: 1.23, 95% CI: 1.06-1.43) and CVD (RR: 1.14, 95% CI: 0.99-1.32).(Strazzullo, D'Elia, Kandala, & Cappuccio, 2009) On the other hand, a meta-analysis of 7 RCTs comparing dietary salt reduction with control/no intervention in normotensive and hypertensive adults showed no benefit of reducing salt intake on CVD events and deaths.(Taylor, Ashton, Moxham, Hooper, & Ebrahim, 2011) However, after excluding a trial including patients with heart failure, another analysis showed that the small reduction in daily salt intake of 2.0-2.3 g significantly reduced CV events by 20%.(F. J. He & MacGregor, 2011)

In this context, it is recommended that the adult population should decrease their salt intake to 6 g/day (2.4 g of sodium/day) which is the equivalent of one level teaspoon.(USDA., 2015)

1.4.7 Fruits and vegetables

Patients should be counseled to consume 2.5 servings of vegetables and 2 servings of fruits daily for a 2000-calorie diet.(USDA., 2015) Fruits and vegetables are a rich source of fiber and essential vitamins and minerals, as well as carbohydrates with a low GI.(USDA., 2015)

Large prospective cohorts have demonstrated that higher total fruit, vegetable and legume intake is inversely associated with major CVD, MI, stroke, CV mortality, non-cardiovascular mortality and total mortality.(Crowe et al., 2011; Du et al., 2016; Miller et al., 2017) A meta-analysis of 16 prospective cohort studies (n=833,234) reported that each serving of fruit and vegetables (up to five servings a day) was associated with a lower risk of all-cause mortality

(HR: 0.95, 95% CI: 0.92-0.98) and CV mortality (HR: 0.96, 95% CI: 0.92-0.99).(X. Wang et al., 2014) An other meta-analysis confirmed the beneficiary effects of fruits and vegetables on mortality, but also on CHD (RR per 200 g/day: 0.92 95% CI: 0.90-0.94), stroke (RR per 200 g/day: 0.84, 95% CI: 0.76-0.92) and total CVD incidence (RR per 200 g/day: 0.92, 95% CI: 0.90-0.95)(Aune et al., 2017) Similar associations were observed for fruits and vegetables separately, whereas reductions in risk were observed up to 800 g/day for CV outcomes.(Aune et al., 2017) Moreover, the intake of apples, pears, citrus fruits, along with green leafy vegetables, cruciferous vegetables, and salads were inversely associated with CVD.(Aune et al., 2017)

1.4.8 Grains

Individuals should consume at least one-half of all grains as whole grains (ie, three or more ounces of whole grain for a 2000-calorie diet) and replace refined grains with whole grains wherever possible.(USDA, 2015) Foods made from wheat, oats, rice, cornmeal or barley are all grain products.(USDA, 2015) Breads, breakfast cereals, oatmeal, tortillas, and pasta are common types of food made from grain.(USDA, 2015) Refined grains (ie, white rice, white bread, refined and sweetened cereals) have bran and germ removed during processing, whereas whole-grain foods, such as brown rice, whole-wheat bread, whole-grain cereal and oatmeal, are a good source of fiber and other nutrients and are considered carbohydrates with a lower GI.(USDA, 2015)

A meta-analysis of 185 prospective studies and 58 RCTs (n=4,635) suggested a 15-30% decrease in all-cause and CV mortality, along with CHD and stroke incidence when comparing the highest dietary fiber consumers with the lowest consumers.(Reynolds et al., 2019) A similar beneficial effect was noticed by the RCTs regarding the effect of whole grains on BP and TC.(Reynolds et al., 2019)

1.4.9 Diaries

The recommended daily consumption of dairy products are three cups for a 2000-calorie diet.(USDA, 2015) The dairy food group is composed of milk and foods made from milk, such as cheese, yogurt and milk-based desserts (ie, pudding, frozen yogurt, ice cream).(USDA, 2015) Dairy products are a good source of protein, calcium, vitamin D, and potassium.(USDA, 2015)

Dairy consumption may reduce CVD risk. One meta-analysis of 10 cohort studies demonstrated that milk drinking may be associated with a small reduction in risk of CHD (RR: 0.87, 95% CI 0.74-1.03) and ischemic stroke (RR: 0.84, 95% CI: 0.78-0.90).(Elwood, Pickering, Hughes, Fehily, & Ness, 2004) In a subsequent large, prospective cohort study (n=136,000) consumption of higher amounts of dairies (more than two servings per day versus no intake) was associated with a reduction in total mortality (HR 0.83, 95% CI: 0.72-0.96), major events of CVD (HR: 0.78, 95% CI: 0.67-0.90) and stroke (HR: 0.66, 95% CI: 0.53-0.82).(Dehghan et al., 2018)

1.4.10 Protein rich foods

Individuals should be advised to consume 2-3 servings of protein-rich foods daily for a 2000-calorie diet.(USDA, 2015) Healthy protein-rich foods include seafood, poultry, beans, peas, nuts and seeds.(USDA, 2015)

Red and processed meat

Prospective cohort studies have demonstrated that increased consumption of red and processed meat are associated with an increased risk of DM, CHD, stroke and increased CVD-related or total mortality.(Abete, Romaguera, Vieira, Lopez de Munain, & Norat, 2014; Feskens, Sluik, & van Woudenbergh, 2013; Kaluza, Wolk, & Larsson, 2012; Micha, Wallace, & Mozaffarian, 2010) However, interventions aiming to reduce red and processed meat consumption (<3 servings weekly) has been associated with a week impact on CV outcomes.(Vernooij et al., 2019; Zeraatkar, Han, et al., 2019; Zeraatkar, Johnston, et al., 2019)

Fish

One to two servings of oily fish per week is suggested for most adults. In a meta-analysis of 11 prospective cohort studies (n= 408,305), fish consumption ≥4 times a week was associated with a decreased ACS risk (RR: 0.79, 95% CI: 0.70-0.89) with a dose-response relationship (each additional 100 g serving/week associated with RR: 0.95, 95% CI: 0.92-0.97).(Leung Yinko, Stark, Thanassoulis, & Pilote, 2014)

Nuts

Nut consumption is associated with lower CVD risk. An analysis including 76,364 women from the Nurses' Health Study (1980 to 2012), 92,946 women from the Nurses' Health Study II (1991 to 2013) and 41,526 men from the Health Professionals Follow-Up Study (1986 to 2012) found that the risk of MI or stroke was reduced among participants who consumed nuts >5 times per week compared with those rarely eating nuts (HR: 0.86, 95% CI: 0.79-0.93).(Guasch-Ferre et al., 2017) Peanuts, tree nuts, and walnuts were all associated with similar reductions in CVD risk.(Guasch-Ferre et al., 2017)

1.4.11 Beverages

Alcohol

Moderate drinking is defined as having up to 1 drink per day for women and up to 2 drinks per day for men; this definition refers to the amount of alcohol consumed on any single day and is not intended as an average over several days.(USDA, 2015) Available evidence suggests that moderate alcohol consumption is associated with CV benefit which is attributed to the antioxidant, antithrombotic, anti-inflammatory effects of alcohol.(Piano, 2017) No long-term RCTs evaluating alcohol consumption have been performed and the available evidence is mainly derived from observational studies. Several prospective cohort studies suggest that light to moderate alcohol consumption decreases CHD risk by 40-70%, when compared with drinking no alcohol or with heavy alcohol intake.(O'Keefe, Bybee, & Lavie, 2007) A meta-analysis including 84 observational studies demonstrated that relative to nondrinkers, alcohol drinkers had lower CVD mortality risk (RR: 0.75, 95% CI: 0.70-0.80) CHD mortality risk (RR: 0.75, 95% CI: 0.68-0.81) and incident CHD risk (RR:0.71, 95% CI: 0.66-0.77).(Ronksley, Brien, Turner, Mukamal, & Ghali, 2011) In a population-based cohort study conducted in United Kingdom and including approximately two million adults aged ≥30 years old without CVD, 5.9% of those developed CVD after a median follow-up of 6 years.(Bell et al., 2017) Moderate drinking compared with no drinking was associated with an increased risk of multiple CVD outcomes, including unstable angina, MI, CHD death, heart failure, ischemic stroke and PAD, whereas heavy drinking was generally associated with worse CV outcomes.(Bell et al., 2017)

Sweetened beverages

The consumption of soft drinks and other sweetened beverages (ie, fruit drinks, sports drinks and energy drinks) should be discouraged, since they are a major source of added refined sugar and calories in diet.(USDA, 2015)

In addition to excess weight and obesity, intake of sugar-sweetened beverages has been found to increase the risk of CHD, DM, hypertension and MetS.(de Koning et al., 2012; Imamura et al., 2015; Xi et al., 2015)

Coffee

Moderate coffee consumption (three to five 8 oz cups/day or providing up to 400 mg/day of caffeine) can be incorporated into healthy eating patterns.(USDA, 2015)

No adverse impact of caffeine or caffeinated beverage consumption on CVD risk has been noticed in many large observational studies.(Kleemola, Jousilahti, Pietinen, Vartiainen, & Tuomilehto, 2000; Lopez-Garcia et al., 2006) A meta-analysis of 36 prospective cohorts including nearly 1.3 million individuals and evaluating the relationship between coffee consumption and CVD risk (a composite of CHD events, stroke, heart failure, and CVD mortality) found a significant nonlinear relationship.(Ding, Bhupathiraju, Satija, van Dam, & Hu, 2014) Compared with individuals consuming no coffee, the RR of CVD was 0.95 (95% CI: 0.87-1.03) for those who consumed a median of five cups per day, 0.85 (95% CI: 0.80-0.90) for those who consumed a median of 3.5 cups per day and 0.89 (95% CI: 0.84-0.94) for those who consumed a median of 1.5 cups per day.(Ding et al., 2014)

1.4.12 Dietary patterns

Many different types of diets have been evaluated for their overall health effects, including impact on CVD, DM, hypertension, cancer and mortality.(WHO, 2018) In addition, several types of diets have been studied for effects on weight reduction, including low-calorie, low-fat, low-carbohydrate, high-protein and portion-controlled diets.(WHO, 2018) Outside of overweight and obese populations, there are few well-designed prospective cohort studies or RCTs comparing different diets. Current guidelines for a healthy diet emphasize on limiting the intake of saturated and trans fatty acids, free sugars and salt, while increasing the intake of fruits, vegetables, legumes, nuts and whole grains.(WHO, 2018; USDA, 2015)

A large cohort study examined the association of dietary modifications made by individuals during a 12-year period with all-cause mortality during the next 12 years.(Sotos-Prieto et al., 2017) Those who improved their diet quality assessed using the Alternative Healthy Eating Index-2010 score, the Alternative Mediterranean Diet score or the DASH score had a significantly lower all-cause mortality compared with individuals who did not change their diet (RR reductions ranging from 9-16%).(Sotos-Prieto et al., 2017)

Among the available diets, low-cholesterol, DASH and Mediterranean diets have been associated with CVD.

Low-cholesterol diet

In a prospective cohort study (using pooled data from 6 studies), over 29,000 American adults without CVD at baseline were followed for a median of 17.5 years.(Zhong et al., 2019) Each additional 300 mg of dietary cholesterol consumed per day was associated with a moderately increased CVD risk (HR: 1.17, 95% CI: 1.09-1.26) and all-cause mortality (HR: 1.18, 95% CI: 1.10-1.26), whereas egg consumption was not associated with this increased risk.(Zhong et al., 2019)

DASH diet

The DASH diet is comprised of 4-5 servings of fruit, 4-5 servings of vegetables, 2-3 servings of low-fat dairy per day and <25% dietary fat intake.(USDA, 2015)

The DASH diet has been studied in both normotensive and hypertensive populations and found to lower systolic and diastolic BP more than a diet rich in fruits and vegetables alone.(Appel et al., 1997) The combination of low-sodium and DASH diet resulted in further BP reduction, comparable with those observed with antihypertensive agents.(Sacks et al., 2001)

The DASH diet has also been associated with a lower DM and CVD risk.(Fung et al., 2008; Salehi-Abargouei, Maghsoudi, Shirani, & Azadbakht, 2013; Schwingshackl, Bogensberger, & Hoffmann, 2018) A meta-analysis of 6 studies showed that imitating a DASH-like diet can significantly reduce CVD (RR: 0.80, 95% CI: 0.74-0.86), CHD (RR: 0.79, 95% CI: 0.71-0.88), stroke (RR: 0.81, 95% CI: 0.72-0.92) and heart failure (RR: 0.71, 95% CI: 0.58-0.88) risk.(Salehi-Abargouei et al., 2013)

Mediterranean diet

There is no single definition of a Mediterranean diet, but such a diet is typically high in fruits, vegetables, whole grains, beans, nuts and seeds, includes olive oil as an important source of monounsaturated fat and allows low to moderate wine consumption.(Bach et al., 2006) It generally includes low to moderate amounts of fish poultry and dairy products, with little red meat.(Bach et al., 2006)

A plethora of observational studies have demonstrated that Mediterranean diet is associated with lower overall and CV mortality.(Ahmad et al., 2018; Panagiotakos et al., 2015; Paterson et al., 2018; Sofi, Cesari, Abbate, Gensini, & Casini, 2008) On the other hand, in a meta-analysis of randomized trials including the large PREDIMED trial (Estruch et al., 2018), Mediterranean diet reduced the risk of stroke compared with low-fat diet (HR: 0.60, 95% CI: 0.45-0.80) but did not reduce the incidence of CV or overall mortality.(Rees et al., 2019)

1.5 Lipid management with diet or dietary supplements

Improvement in serum lipids can be achieved through lifestyle changes including dietary modification.(Varady & Jones, 2005; Vogel et al., 2005) A dietary approach to lipid management, including an overall change in dietary pattern, the use of specific dietary components and the use of supplements, may be used with or without adjunctive pharmacotherapy to achieve lipid goals.(Mach et al., 2020)

1.5.1 Mediterranean diet

Following a Mediterranean diet may lead to TC reduction. A meta-analysis of 6 RCTs comparing Mediterranean with low-fat diet in 2,650 overweight/obese individuals, a Mediterranean diet led to a greater reduction in TC (-7.4 mg/dL, 95% CI: -10.3 to -4.4), but a non-significant reduction in LDL-C (-3.3 mg/dL, 95% CI: -7.3 to +0.6 mg/dL).(Nordmann et al., 2011) Adherence to Mediterranean diet can also improve TG levels, particularly in individuals with DM.(Estruch et al., 2006)

A recent meta-analysis of RCTs showed that Mediterranean dietary intervention versus no intervention or minimal intervention for primary prevention reduced TC (-0.16 mmol/L, 95%: CI

-0.32 to 0.00), but there was low or very low-quality evidence of little or no effect on LDL-C, HDL-C or TG.(Rees et al., 2019) When compared with other dietary interventions in the setting of primary CV prevention, Mediterranean diet was associated with a possible small reduction in LDL-C (-0.15 mmol/L, 95% CI: -0.27 to -0.02) and TG (-0.09 mmol/L, 95% CI -0.16 to -0.01), but little or no effect on TC or HDL-C.(Rees et al., 2019)

1.5.2 DASH diet

Adhering to a DASH diet may improve serum lipid profile. A meta-analysis including 20 RCTs with 1,917 participants demonstrated that DASH diet reduces TC (-0.20 mmol/L, 95% CI: -0.31 to -0.10) and LDL-C (-0.10 mmol/L, 95% CI: -0.20 to -0.01), but TG and HDL-C remained unchanged.(Siervo et al., 2015)

Modification of the DASH diet results in further improvements in serum lipids. For instance, in the OmniHeart trial, the carbohydrate content of the DASH diet was reduced (from 58 to 48% of energy) and partially replaced with either protein or unsaturated fat.(Appel et al., 2005) Compared with the traditional DASH diet, the protein-replaced diet (25 vs 15% of energy) further decreased LDL-C by 3.3 mg/dL, HDL-C by 1.3 mg/dL and TG by 15.7 mg/dL; the unsaturated fat-replaced diet (31 vs 21 % of energy) had no effect on LDL-C, but lowered TG by 9.6 mg/dL and increased HDL-C by 1.1 mg/dL.(Appel et al., 2005)

1.5.3 Vegetarian diet

In addition to a vegetarian diet pattern (a diet that excludes only animal flesh), there are many other variations of meat-restricted diets (eg, vegan, ovovegetarian, lactovegetarian, lacto-ovovegetarian) that may improve serum lipid profiles. A meta-analysis of 11 trials comparing meat-restricted with omnivorous diets, a vegetarian diet lowered TC (-13.9 mg/dL, 95% CI: -21.3 to -6.6 mg/dL), LDL-C (-13.1 mg/dL, 95% CI: -22.0 to -4.2 mg/dL), and HDL-C (-3.9 mg/dL, 95% CI: -5.4 to -2.3 mg/dL), but there was no reduction in serum TG.(F. Wang et al., 2015)

1.5.4 Low-carbohydrate diet

Low-carbohydrate diets vary in the quantity and types of carbohydrate they contain, but in general, such a diet is limited to less than 130 g/day of carbohydrates (with less than 60 g/day considered a very low carbohydrate diet).(Shai et al., 2008)

A RCTs comparing three dietary patterns (low-fat, Mediterranean and low-carbohydrate diets) in over 300 overweight adults, demonstrated that weight loss and HDL-C increase occurred in all groups at 24 months, with the largest weight loss and HDL-C increase noticed in those adhering to the low-carbohydrate diet (-5.5 kg and 8.4 mg/dL, respectively).(Shai et al., 2008) Those on the Mediterranean and low-carbohydrate diets had the largest reduction in TG (-21.8 and -23.7 mg/dL, respectively).(Shai et al., 2008)

1.5.5 Diet low in trans fatty acids

Replacement of dietary trans fatty acids with cis-polyunsaturated fatty acids lowers TC, LDL-C, TG, apoB and raises HDL-C.(Judd et al., 1994; Lichtenstein, Ausman, Jalbert, & Schaefer, 1999)

1.5.6 Dietary fiber

The consumption of certain soluble fibers, such as psyllium, pectin, wheat dextrin, certain beans (eg, navy, pinto and black beans), lentils, nuts and oat products, can produce a TC and LDL-C reduction. Fiber is effective whether added to the diet as a supplement or used as a component of a dietary modification plan (ie, substituting whole grains for processed carbohydrates).(USDA, 2015)

Indeed, a meta-analysis of 28 RCTs with 1,924 patients with both normal and elevated cholesterol levels, the addition of 10.2 g/day of psyllium lowered LDL-C by an average of 12.8 mg/dL.(Jovanovski et al., 2018) An older meta-analysis demonstrated that increased consumption of soluble fiber reduced both TC and LDL-C.(Brown, Rosner, Willett, & Sacks, 1999) For every gram increase in dietary soluble fiber, LDL-C decreased by an average of 2.2 mg/dL.(Brown et al., 1999) TC decreased by fiber type: oat-based fibers (-0 to -18%); psyllium (-3 to -17%); pectin (-5 to -16%) and guar gum (-4 to -17%).(Brown et al., 1999) No change in TG and HDL-C was noticed.(Brown et al., 1999) In another meta-analysis of RCTs, whole-grain diets reduced LDL-C and TC, with whole-grain oats having the greatest effect on TC levels (average reduction of 6.6 mg/dL).(Hollaender, Ross, & Kristensen, 2015) TG and HDL-C were not changed. (Hollaender et al., 2015)

1.5.7 Nuts

The consumption of nuts that are high in MUFAs or PUFAs (particularly walnuts, almonds, pistachios, macadamia nuts, pecans, and hazelnuts) may improve serum cholesterol.

RCTs have demonstrated that walnuts, which are rich in PUFAs and especially in omega-3 fatty acids, have a beneficial effect on serum lipids.(Sabate et al., 1993; Zambon et al., 2000) In a trial comparing a Mediterranean diet with a similar diet in which walnuts replaced 35% of the energy from MUFAs, those on the walnut-replaced diet experienced a greater TC (-10.8 mg/dL, 95% CI: -16.8 to -4.8 mg/dL) and LDL-C reduction (11.2 mg/dL, 95% CI: -16.3 to -6.1 mg/dL).(Zambon et al., 2000) In another trial, a NCEP Step I diet was compared with a similar diet in which walnuts accounted for 20% of calories.(Sabate et al., 1993) Those on the walnut-rich diet had a greater reduction in TC (22.4 mg/dL, 95% CI: -28 to -17 mg/dL), LDL-C (18.2 mg/dL, 95% CI: -23.2 to -13.2 mg/dL) and HDL-C (-2.3 mg/dL, 95% CI: -3.9 to -0.7 mg/dL), but no change in TG.(Sabate et al., 1993)

Similarly, improvement in cholesterol was also seen with the consumption of almonds, which are high in MUFAs and fiber.(Lee et al., 2017) A trial including 30 overweight or obese adults showed that daily consumption of almonds (42 g/day) reduced TC and LDL-C by 4% and 7%, respectively, whereas no change in HDL-C or TG was found.(Lee et al., 2017)

In addition to walnuts and almonds, similar lipid-lowering effects have been noticed with the consumption of other nuts including pistachios, hazelnuts, pecans, macadamia nuts and pistachios.(Gebauer et al., 2008; Sabate, Oda, & Ros, 2010) Indeed, in the PREDIMED trial, a Mediterranean diet supplemented with nuts (30 g of nuts, including 15 g walnuts, 7.5 g hazelnuts and 7.5 g almonds) lowered TC, LDL-C and TG compared with a control diet.(Estruch et al., 2018)

1.5.8 Soy

Soy is an excellent source of protein and also contains isoflavones, which are phytoestrogens. Isoflavones have some properties similar to estrogen and may have a small effect on cholesterol levels and inhibition on LDL oxidation.(Lissin & Cooke, 2000)

Although previous evidence had suggested important lipid benefits with soy consumption (J. W. Anderson, Johnstone, & Cook-Newell, 1995; Crouse et al., 1999; Teixeira et al., 2000), a subsequent systematic review concluded that the benefits of soy consumption were small and that isoflavones alone had no beneficial effect.(Sacks et al., 2006) Nevertheless, when large amounts of soy protein (average 50 g/day) were substituted for other dietary proteins, LDL-C decreased by 3%, but there was no effect on HDL-C, TG or apoA.(Sacks et al., 2006) Similarly, a recent meta-analysis of 46 RCTs of soy consumption, confirmed the modest benefits of soy intake on TC and LDL-C.(D. J. A. Jenkins et al., 2019)

1.5.9 Plant sterols and stanols

Plants contain a number of sterols, stanols and their esters that can lower serum cholesterol; these compounds are similar in chemical structure to cholesterol, differing in their side chain configuration.(Gylling et al., 2014) Plant sterols differ from plant stanols in that the B ring contains an unsaturated bond.(Gylling et al., 2014) The mechanism by which sterols and stanols lower cholesterol involves inhibition of cholesterol absorption, mostly through the disruption in intraluminal solubilization.(Gylling et al., 2014)

As shown in Table 7, there are naturally occurring sterols and stanols in nuts, legumes, whole grains, fruits, vegetables and plant oils.(Gylling et al., 2014) In addition, a number of manufactured products enriched with plant sterols and stanols are commercially available.(Gylling et al., 2014) The margarines containing these compounds have been available the longest and are the most studied.(Gylling et al., 2014)

Data from observational studies are inconsistent. Large epidemiological studies have observed that naturally occurring dietary plant sterol intake is inversely related to plasma TC and LDL-C levels.(Gylling et al., 2014) However, in a well-controlled study in healthy subjects, low (126 mg plant sterols/2000 kilocalories) or high intake of plant sterols (449 mg plant sterols/2000 kilocalories) did not affect plasma LDL-C concentrations in spite of modulating cholesterol metabolism.(Lin et al., 2010) Furthermore, even at the highest levels of dietary intake, plant sterols/stanols occurring naturally in the diet have a modest hypocholesterolemic effect.(Lin et al., 2010) On the other hand, RCTs and several meta-analyses have confirmed the LDL-C

lowering effects of foods with added plant sterols/stanols. Meta-analyses of RCTs have demonstrated that phytosterols intakes of 0.6-3.3 g/d reduce LDL-C concentrations by 6-12%.(Demonty et al., 2009; Ras, Geleijnse, & Trautwein, 2014)

Plant sterols and stanols may also lower TG in normotriglyceridemic and hypertriglyceridemic individuals by 0.8-7% and 11-28%, respectively.(Ras et al., 2014; Rideout, Chan, Harding, & Jones, 2009)

Table 7 *Plant sterol and plant stanol contents in different foods*

Food item	Plant Sterols	Plant stanols	Food item	Plant Sterols	Plant stanols
Vegetable oils			**Vegetables**		
Corn oil	686-952	23-33	Broccoli	39	2
Rapeseed oil (canola oil)	250-767	2-12	Cauliflower	18-40	Traces
Soybean oil	221-328	7	Carrot	12-16	Traces
Sunflower oil	263-376	4	Lettuce	9-17	0.5
Olive oil	144-193	0.3-4	Potato	7	0.6
Palm oil	60-78	Traces	Tomato	7	1
Cereals			**Fruits and berries**		
Corn	66-178	-	Avocado	75	0.5
Rye	71-113	12-22	Passion fruit	44	Not detected
Wheat	45-83	17	Raspberry	27	0.2
Barley	80	2	Orange	24	Not detected
Millet	77	-	Apple	12-18	0.8
Rice	72	3	Banana	12-16	Not detected
Oats	35-61	1			
Nuts					
Peanuts	320	-			
Almond	143	-			

Data are given as mg/100 g (dry weight, either range or mean value).

1.5.10 Tea

Consumption of tea and tea products may lower serum cholesterol; in a meta-analysis of 11 RCTs (n=821), consumption of green or black tea reduced LDL-C (-19 mg/dL, 95% CI: -24 to -14 mg/dL), but had no effect on HDL-C.(Hartley et al., 2013)

1.5.11 Polyphenols

Polyphenols, substances with antioxidant effects, are found primarily in plants (and in plant-based foods), such as tea, coffee, cocoa, olive oil and red wine and include flavonoids and flavonoid derivatives, lignans, phenolic acids and stilbenes.(Hollman et al., 2011; Tangney & Rasmussen, 2013)

There is some evidence that consumption of polyphenols in foods has favorable effects on serum lipids. A trial including 200 healthy individuals and comparing the effects of virgin olive oil (high in polyphenols), refined olive oil (low in polyphenols) and a mixture of the two (with intermediate polyphenol content) on serum lipids showed dose-response effects on both LDL-C and HDL-C; high-polyphenol olive oil raised HDL-C and lowered LDL-C more than low-polyphenol olive oil.(Covas et al., 2006)

Resveratrol, a stilbene that occurs naturally in several plants, including red grape skin, blueberries, peanuts and cocoa, may have beneficial lipid effects; in a trial of adults with MetS, consumption of one cup of blueberries daily for 6 months increased HDL-C, HDL particle density and apoA-I.(Curtis et al., 2019)

1.5.12 Omega-3 fatty acids

Consumption of omega-3 fatty acids mainly reduce TG but may also affect (raise or lower) cholesterol levels.

In a meta-analysis of 55 RCTs, each 1 g/day increase in EPA/DHA reduced TG by 5.9 mg/dL, with the effect being stronger in case of higher baseline TG; above the median TG level of 83 mg/dL, each 1 g/day EPA/DHA reduced triglycerides by 8.4 mg/dL.(Mozaffarian & Wu, 2011)

In addition, omega-3 fatty acids may also affect LDL and HDL-C levels, although the results are mixed and dependent upon the source and composition of the omega-3 fatty acid consumed. In a meta-analysis of 7 trials (n= 662), krill oil supplementation (1 to 4 g/day for 24 weeks) reduced LDL-C (-15.5 mg/dL, 95% CI: -28.4 to -2.6 mg/dL) and TG (-14.0 mg/dL, 95% CI: -21.4 to -6.7 mg/dL).(Ursoniu et al., 2017) In addition, plasma concentrations of HDL-C were increased (6.6 mg/dL, 95% CI: 2.3 to 11.0 mg/dL).(Ursoniu et al., 2017) Another meta-analysis including 28 RCTs showed that the consumption of flaxseeds (whole, ground, or defatted, 20 to 50 g/day) reduced TC (-7.3 mg/dL, 95% CI: -11.2 to -3.5 mg/dL) and LDL-C (-6.2 mg/dL, 95% CI: -9.7 to -2.3 md/dL), but no effect on TG or HDL-C was found.(Pan, Yu, Demark-Wahnefried, Franco, & Lin, 2009) Of note though, the consumption of flaxseed oil had no effect on serum lipids.(Pan et al., 2009)

1.5.13 Red yeast rice

Red yeast rice is a fermented rice product which is often taken as a supplement and can improve serum cholesterol, since it contains varying amounts of monacolins that have HMG CoA reductase inhibitor activity, like statins.(Patrick & Uzick, 2001) In addition, red yeast rice includes other active ingredients that may lower cholesterol, such as sterols (beta-sitosterol, campesterol, stigmasterol, sapogenin), isoflavones and MUFAs.(Heber et al., 1999)

In a trial including 62 statin-intolerant patients, treatment with red yeast rice (1,800 mg twice daily for 24 weeks) was well tolerated and achieved greater reductions in both TC (15 vs 5%) and LDLC (21 vs 9%) compared with placebo, but had no effect on HDL-C.(Becker et al., 2009)

1.5.14 Berberine

Berberine is an alkaloid found in the root, fruit or bark of a number of plants such as goldenseal, Oregon grape, barberry and tree turmeric and reduces serum cholesterol levels through several mechanisms, including reduction of intestinal cholesterol absorption, enhanced fecal cholesterol excretion (X. Y. Li et al., 2015), inhibition of PCSK9 (H. Li et al., 2009) and upregulation of LDL-C.(Abidi, Zhou, Jiang, & Liu, 2005) A meta-analysis of 6 RCTs including 229 patients with hyperlipidemia demonstrated that berberine supplementation (900-1,500 mg/day) improved TC (-25.5 mg/dL, 95% CI: -39.4 to -12 mg/dL), LDL-C (-25.1 mg/dL, 95% CI: -

29 to -21.7 mg/dL) and TG (-34.5 mg/dL, 95% CI: -52.3 to -16.8) when compared with placebo or lifestyle modification.(Lan et al., 2015)

1.5.15 Green tea catechins

Consumption of green tea along with the corresponding supplements have a beneficial effect on lipids. Indeed, in a year-long RCT (n=1,075) green tea catechin supplements (1,315 mg catechins/day) reduced TC and LDL-C and increased TG, but had no effect on HDL-C.(Samavat et al., 2016) These findings are consistent with those of previous trials and meta-analyses.(Mielgo-Ayuso et al., 2014; Onakpoya, Spencer, Heneghan, & Thompson, 2014)

CHAPTER 2 AIMS AND OUTLINE

Despite the revolution evolved in the setting of CV prevention and the plethora of therapeutic options confronting CV risk factors being available during the last decade, CVD remains the leading cause of mortality in the developed countries.(Benjamin et al., 2019; Timmis et al., 2018) Even FH, the most commonly inherited metabolic disorder associated with premature CHD, remains underdiagnosed and undertreated.(Nordestgaard et al., 2013) Apart from the development of novel treatments, diet continuous to play a key role in this therapeutic gap of CV prevention.(Mozaffarian, 2016)

Current guidelines for CV prevention emphasize on lifestyle and dietary modifications. (Mach et al., 2020) Adherence to dietary patterns, such as Mediterranean diet, DASH diet, vegetarian (or other meat restricted) diet, low-carbohydrate diet and low trans fatty acid diet improve serum lipids in patients with dyslipidemia. (Mozaffarian, 2016; Zarraga & Schwarz, 2006) Such dietary changes, particularly in patients with poor baseline diets, can reduce LDL-C by as much as 30%.(Zarraga & Schwarz, 2006) For individuals who are unwilling or unable to make sweeping changes to their overall dietary pattern, the inclusion of specific dietary components known to

improve lipids and the replacement of those with detrimental effects on lipids is suggested.(Mach et al., 2020) In addition, there are several dietary supplements that have beneficial effects on lipids, such as omega-3 fatty acids, red yeast rice, berberine and green tea extracts.(Mach et al., 2020) Table 8 summarizes the currently available evidence on the influences of lifestyle changes and functional foods on lipoproteins.(Mach et al., 2020)

As LDL reductions ≥50% are required for treatment, diet management in FH has been considered a secondary therapy. Based on the current guidelines for the management of dyslipidemias, dietary interventions, such as the manipulation of different types of fatty acids, increasing dietary intake of soluble fiber and increasing the intake of certain dietary components (ie. soy protein, plant sterols and stanols, omega-3 fatty acids) are recommended in patients with FH who cannot start (ie. children) or tolerate lipid-lowering therapy (ie. statin intolerant patients).(Mach et al., 2020) Nevertheless, the majority of these interventions have not been adequately assessed and consensus has yet to be reached on the most appropriate dietary treatment for FH.(Gidding, 2019)

The aim of this work was to assess the CV effectiveness of the currently recommended cholesterol lowering diet and other forms of dietary intervention in children and adults with FH.

In this context, we investigated in individuals with FH:

- Whether manipulating the fat, protein or carbohydrate content of the diet influences serum lipids and CVD incidence
- Whether omega-3 fatty acids affect serum lipids and CVD incidence
- Whether the addition of plant sterols to the background diet affects serum lipids and CVD incidence
- Whether the addition of plant stanols to the background diet affects serum lipids and CVD incidence
- Whether the addition of soy protein to the background diet affects serum lipids and CVD incidence
- Whether adding dietary fibers such as barley, oat bran, rice bran, flax seeds or psyllium affects serum lipids and CVD incidence

Table 8 *Impact of specific lifestyle changes on lipid levels*

	Magnitude of the effect
I. Lifestyle interventions to reduce TC and LDL-C levels	
Avoid dietary trans fats	5-10%
Reduce dietary saturated fats	5-10%
Increase dietary fiber	5-10%
Use functional foods enriched with phytosterols	5-10%
Use red yeast rice nutraceuticals	5-10%
Reduce excessive body weight	5-10%
Reduce dietary cholesterol	≤5%
Increase habitual physical activity	≤5%
II. Lifestyle interventions to reduce TG-rich lipoprotein levels	
Reduce excessive body weight	≤5%
Reduce alcohol intake	≥10%
Increase habitual physical activity	5-10%
Reduce total amount of dietary carbohydrates	5-10%
Use supplements of n-3 polyunsaturated fats	5-10%
Reduce intake of mono- and disaccharides	5-10%
Replace saturated fats with mono- or polyunsaturated fats	≤5%
III. Lifestyle interventions to increase HDL-C levels	
Avoid dietary trans fats	5-10%
Increase habitual physical activity	≥10%
Reduce excessive body weight	5-10%
Reduce dietary carbohydrates and replace them with unsaturated fats	5-10%
Modest consumption in those who take alcohol may be continued	5-10%
Quit smoking	≤5%

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides

CHAPTER 3 METHODS

3.1 Eligibility criteria

Types of studies

Published RCTs were included in the present meta-analysis. Trials using quasi-randomization methods were alternatively included in case of sufficient evidence that the treatment and comparison groups were comparable in terms of clinical and nutritional status.

Study participants

Studies including children and adults with FH (alternative named as inherited dyslipidemia IIa) were considered eligible for the present meta-analysis. Trials including patients with FH along with others not fulfilling the criteria of FH diagnosis were only included if the group of FH individuals was well defined and the results for this group were available.

Interventions

Cholesterol-lowering diet or any other dietary intervention intended to lower serum TC or LDL-C, for a period of at least 3 weeks. RCTs comparing dietary treatment as a control with lipid-

lowering drugs were excluded. However, we included those trials when the only difference between the control and treatment groups was the diet; for instance, in case that a drug treatment alone was compared with the same drug treatment in combination with dietary treatment. Trials where one form of modified dietary intake was compared to another form of dietary intake were included if the comparison was done in a head-to-head comparison.

3.2 Outcomes

Incidence and mortality of total CVD, CHD, stroke or PAD were considered as the primary outcomes of interest in our meta-analysis. The secondary outcomes were the following: TC, TG, HDL-C, LDL-C, VLDL-C, apoA-I, apoB and Lp(a).

3.3 Information sources

Relevant trials were identified by searching US National Library of Medicine National Institutes of Health Metabolism Trials Register (https://www.ncbi.nlm.nih.gov/pubmed) and clinicaltrials.gov.gr (https://clinicaltrials.gov) using the following terms: diet, dietary, plant sterols, stanols, omega-3 fatty acids, fiber and familial hypercholesterolemia. RCTs included in our analysis were also scrutinized for other trials fulfilling our eligibility criteria.

3.4 Data collection and analysis

Selection of studies

At initial review stage and for each update, two authors independently selected the trials to be included in the review.

Data extraction and management

Two review authors (FB and DP) independently extracted data using a pre-designed data extraction form that contained publication details, study population, randomization, allocation concealment, details of blinding measures, description of interventions and results. Any differences between them were resolved by consulting the other review authors (TN and EL).

Due to the different dietary interventions suggested for FH, the trials were divided into the following comparisons:

- Dietary intervention to reduce fat content

- Supplementation with omega-3 fatty acids compared with placebo
- Dietary interventions modifying unsaturated fat content
- Cholesterol-lowering diet compared with dietary interventions increasing intake of plant stanols
- Cholesterol-lowering diet compared with dietary interventions increasing intake of plant sterols
- Dietary interventions increasing intake of plant stanols compared with plant sterols
- Dietary interventions modifying protein content
- Dietary interventions increasing intake of dietary fiber

Outcome data were grouped into those measured at up to one, three, six and twelve months and annually thereafter. However, as was the case, if outcome data were recorded at other time periods (ie. 2, 4, 6, 8 weeks data), then the authors planned to consider examining these as well. A 4-week period is generally the time when the treatment effects of dietary intervention on lipids become visible. In order to see how the effects are maintained, analyses at longer periods are desirable. For the primary outcomes, analyzing the results of longer follow-up is necessary.

In case of duplicate trials, we included the trial with the longest follow-up.

3.5 Assessment of risk of bias in included studies

The following domains were assessed as either low, unclear or high risk of bias: i) sequence generation, ii) allocation concealment, iii) blinding (of participants, personnel and outcome assessors), iv) incomplete outcome data addressed, v) free of selective outcome reporting and vi) free of other bias. Overall, trials were considered at high-risk of bias if we could only assess the majority of domains as having a high or unclear risk. Any differences between FB and DP were resolved by consultation.

3.6 Measurements of treatment effect

No data were available regarding the incident and mortality of CVD. In case of available data for these outcomes, the number of events and the total number randomized in each group would be taken to calculate the odds ratio (OR) and 95% CIs.

Continuous outcomes were analyzed using the mean difference (MD) and associated 95% CIs. In case of different scales of measurement, the standardized mean difference (SMD) would be calculated. When only the standard error (SE) was provided, we converted this to the SD by multiplying the SE by the square root of the number of participants.

3.7 Synthesis of results

Missing data

In order to allow an intention-to-treat analysis, the authors would have sought data on the number of participants with each outcome event, by allocated treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up.

RCTs not reporting the results of the subgroup of FH patients have not been included in the present analysis. The authors were requested to supply these data through electronic communication. At the time of writing this review, these data have not been received.

Assessment of heterogeneity

Heterogeneity between trial results was tested using a standard chi-square test; $p < 0.1$ was considered statistically significant. I^2 statistic was used as a measure of heterogeneity.(Higgins, Thompson, Deeks, & Altman, 2003) This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than chance. The following ranges and descriptions were used:

- 0-40%: might not be important
- 30-60%: may represent moderate heterogeneity
- 50-90%: may represent substantial heterogeneity
- 75-100%: considerable heterogeneity

3.8 Assessment of reporting biases

Publication bias was planned to be assessed with the means of a funnel plot. The primary outcome measure was to be the main outcome for generation of the funnel plot. In the absence of an adequate number of trials reporting the primary outcome, any secondary outcome for which three or more trials were available, would have been used for funnel plot

construction. Outcome reporting bias ideally was assessed by comparing the original trial protocols with the final published papers. In case that the protocols were unavailable, the outcomes that were described as being measured in the 'Methods' section of the final papers were compared with the 'Results' section to identify any outcomes not being reported. Moreover, our clinical knowledge would help us identify any outcomes expected to be measured, but they were not reported.

3.9 Additional analyses

Subgroup analysis and investigation of heterogeneity

In case of observed statistically significant heterogeneity, a random-effect meta-analysis was performed. Otherwise, a fixed-effect model was used.

CHAPTER 4 RESULTS

4.1 Study selection

As shown in Figure 2, of the 1430 references initially identified from the electronic and manual search studies, a total of 17 RCTs were included in the present meta-analysis.

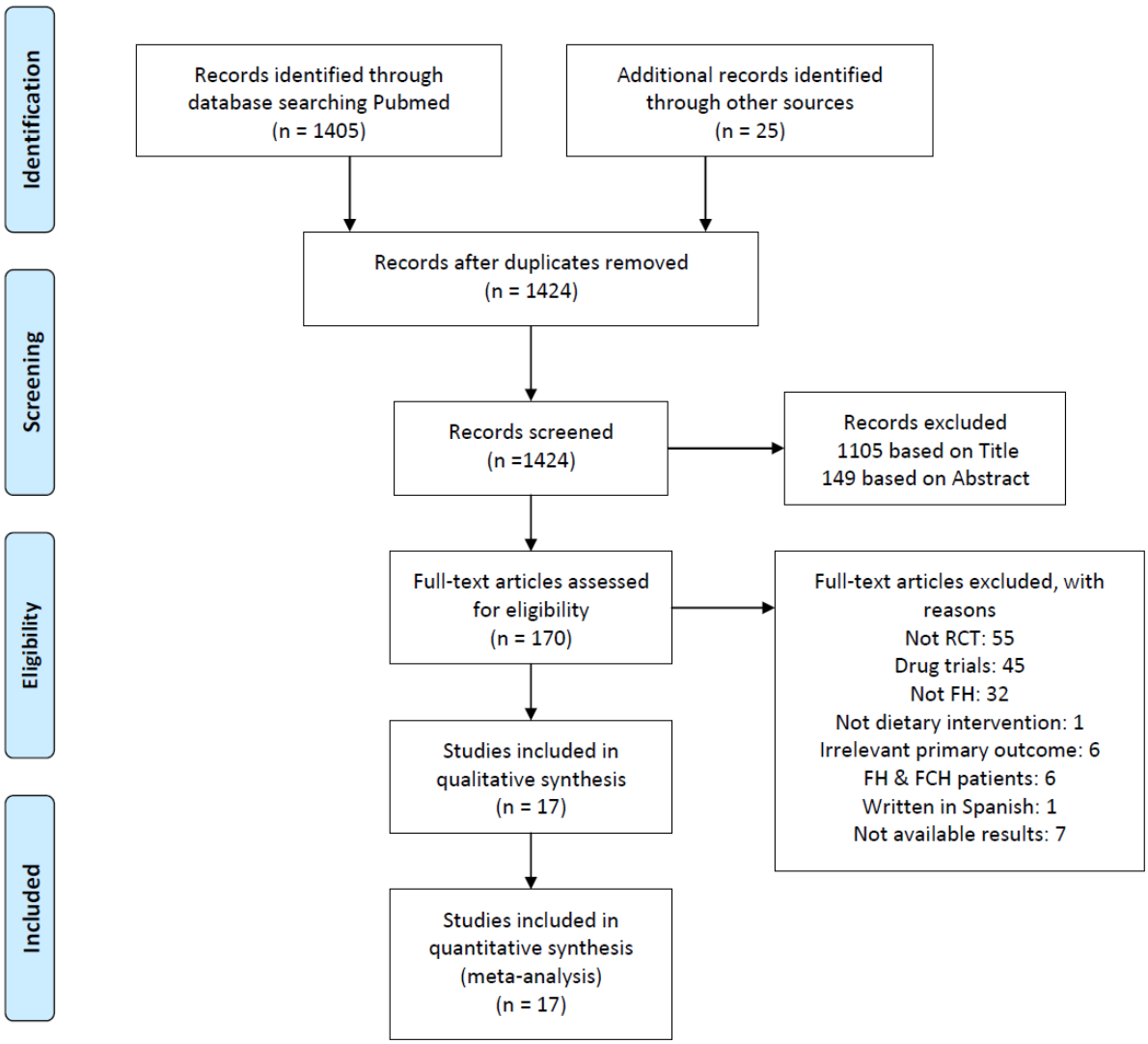


Figure 2 PRISMA flow diagram of study selection

FCH, Familial combined hyperlipidemia; FH, Familial hypercholesterolemia; RCT, Randomized clinical trial

4.2 Study characteristics

The design of the RCTs included in the present meta-analysis, along with their samples and the investigated dietary interventions are demonstrated in Table 9.

Table 9 *Characteristics of the included trials*

Trial	Study design (duration)	Participants	Interventions
Amundsen 2002	Double-blind, placebo-controlled randomized, cross-over (8w)	41 children with FH (aged 10.5 ± 1.7 yrs old)	Low-fat/low-cholesterol diet & 1.60 ± 0.13 g plant sterols in a fortified spread (18.2 ± 1.5 g/d) vs low-fat/low-cholesterol diet & placebo
Balestrieri 1996	Double-blind, randomized, cross-over (4w)	16 adults with FH treated with simvastatin (aged 45.2 ± 15 yrs old)	Cholesterol-lowering diet & 6 g/d fish oil ethyl ester vs cholesterol-lowering diet & placebo (olive oil)
Chan 2016	Open-label, placebo-controlled randomized, cross-over (8w)	22 adults with FH taking lipid-lowering therapy (aged 53.3 ± 3 yrs old)	4 g/d omega-3 fatty acid ethyl ester (46% eicosapentaenoic acid and 38% docosahexaenoic acid) vs placebo
Chisholm 1994	Randomized, cross-over (8w)	19 adults with FH treated with simvastatin (aged 51 ± 10 yrs old)	Low-fat/low-cholesterol diet vs a higher-fat/higher-cholesterol diet
De Jongh 2003	Double-blind, placebo-controlled randomized, cross-over (4w)	41 children with FH (aged 9.2 ± 1.6 yrs old) and 20 controls (aged 8.2 ± 2.2 yrs old)	Low-fat/low-cholesterol diet & 2.3 g plant sterols in a fortified spread (15 g/d) vs low-fat/low-cholesterol diet & placebo
Fuentes 2008	Randomized, cross-over (4w)	30 adults with FH taking lipid-lowering therapy (aged 42 ± 18 yrs old)	4 low-fat diets with different content of cholesterol (<150 or 300 mg/d) and sitosterol (<1 or 2 g/d)
Gustafsson 1983	Randomized, cross-over (3w)	20 hyperlipoproteinemic adults: 6 with type IIa (aged 30-60 yrs old), 8 with type IIb (aged 41-65 yrs old) and 6 with type IV hyperlipoproteinemia (aged 51-66 yrs old)	2 low-cholesterol diets differing in polyunsaturated:saturated fat ratio (2.0 vs 1.3)
Gylling 1995	Double-blind, placebo-controlled randomized, cross-over (6w)	14 children with heterozygous FH (aged 9.1 ± 1.1 yrs old)	Low-fat/low-cholesterol diet & 3 g sitostanol ester dissolved in rapeseed oil margarine vs low-fat/low-cholesterol diet & placebo

Hande 2019	Double-blind, placebo-controlled randomized, cross-over (3m)	34 patients with FH on lipid-lowering treatment (aged 46.6 (18-71) yrs old)	4 g/d omega-3 fatty acids in a 1000 mg capsule consisting of 460 mg of eicosapentaenoic acid and 380 mg of docosahexaenoic acid (administered twice a day) vs placebo (capsules with olive oil)
Helk 2019	Placebo-controlled randomized (13w)	26 children with FH (Aged 8.7 ± 3.8 yrs old)	Diet high in unsaturated fats, low in saturated fats and enriched with soy-protein vs diet high in unsaturated fats and low in saturated fats
Jakulj 2006	Double-blind, placebo-controlled randomized, cross-over (4w)	42 children with FH (aged 9.8 ± 1.5 yrs old)	Low-fat/low-cholesterol diet & 2 g plant stanols in a low-fat fortified yogurt (500 mL/d) vs low-fat/low-cholesterol diet & placebo
Ketomaki 2005	Double-blind randomized, cross-over (4w)	18 adults with FH taking lipid-lowering therapy (aged 48 ± 2 yrs old)	Low-fat diet & 2 g plant stanols (25 g spread/d) vs low-fat diet & 2 g plant sterols (25 g spread/d)
Laurin 1991	Randomized, cross-over (4w)	10 children with FH (aged 8 ± 1 yrs old)	2 different low-fat/low-cholesterol/high-protein diets: about one-third (35%) of the protein energy was consumed as a dairy source, either from cow milk or a soy beverage
Negele 2015	Double-blind, randomized pilot trial (13w)	21 children with FH (aged 11.1 ± 3.4 yrs old)	Low-fat/low-cholesterol diet & monounsaturated fatty acids by rapeseed oil vs low-fat/low-cholesterol diet & polyunsaturated fatty acids by sunflower oil
Neil 2001	Double-blind, placebo-controlled randomized, cross-over (8w)	62 adults with heterozygous FH (30 were statin-treated) (aged 51.6 (33.3-62.3) yrs old)	Low-cholesterol diet & 2.5 g plant sterols in a fortified spread (25 g/d) vs low-cholesterol diet & placebo
Wirth 1982	Randomized cross-over (2m)	12 adults with FH treated with fibrate (aged 51.7 (31-60) yrs old)	Bezafibrate vs bezafibrate & 5.2 g guar
Wolfe 1992	Randomized, cross-over (4-5w)	10 adults with familial hypercholesterolemia (2 of those had possibly FCH) (aged 50 ± 5 yrs old)	Low-fat/low-cholesterol/high-protein (23%) diet vs low-fat/low-cholesterol/low-protein (11%) diet

d, day; FCH, familial combined hyperlipidemia; FH, familial hypercholesterolemia; m, months; w, weeks; yrs, years

The majority of the included studies was double-blind, placebo-controlled and randomized with a cross-over design.(Amundsen, Ose, Nenseter, & Ntanios, 2002; Balestrieri et al., 1996; de

Jongh et al., 2003; Gylling et al., 2014; Hande et al., 2019; Jakulj et al., 2006; H. A. Neil, Meijer, & Roe, 2001) Their duration ranged from 3 to 13 weeks and their samples from 10 to 62 subjects. Seven trials enrolled children fulfilling the criteria of FH (Amundsen et al., 2002; de Jongh et al., 2003; Gylling, Siimes, & Miettinen, 1995; Helk & Widhalm, 2020; Jakulj et al., 2006; Laurin et al., 1991; Negele et al., 2015) Among the rest studies including adults with FH, in 8 RCTs the subjects were also treated with lipid-lowering drugs.(Balestrieri et al., 1996; Chan et al., 2016; Chisholm, Sutherland, & Ball, 1994; Fuentes et al., 2008; Hande et al., 2019; Ketomaki, Gylling, & Miettinen, 2005; H. A. Neil et al., 2001; Wirth, Middelhoff, Braeuning, & Schlierf, 1982)

We report on 8 dietary interventions separately.

- Only one study evaluated the impact of cholesterol-lowering diet in adults with FH, who were treated with simvastatin.(Chisholm et al., 1994)
- Three trials compared the effect of treatment with omega-3 fatty acids in comparison with placebo.(Balestrieri et al., 1996; Chan et al., 2016; Hande et al., 2019) The daily supplementation of omega-3 fatty acids was 5.1 g with a ratio of EPA/DHA of 1:1 in the oldest trial (Balestrieri et al., 1996), whereas the treatment arm in the rest RCTs comprised of 4 g/d of EPA/DHA (46% EPA and 38% DHA).(Chan et al., 2016; Hande et al., 2019). All of these trials included adults taking lipid-lowering therapy (Balestrieri et al., 1996; Chan et al., 2016; Hande et al., 2019), and only one reported that its subjects adhered to cholesterol-lowering diet.(Balestrieri et al., 1996)
- Two trials evaluated the impact of modified fat on FH patients. The former compared 2 low-fat diet regimes enriched with either MUFAs by rapeseed oil or PUFAs by sunflower oil in children with FH. (Negele et al., 2015) The second trial assigned its subjects to 2 cholesterol-lowering diets differing with regard to polyunsaturated:saturated values (2.0 and 1.3 respectively)(Gustafsson, Boberg, Karlstrom, Lithell, & Vessby, 1983)
- Two RCTs investigated the dietary interventions increasing the intake of plant stanols. The first study compared the addition of 3 g sitostanol dissolved in margarine to cholesterol-lowering diet with placebo in children with FH.(Gylling et al., 1995) The second one evaluated the addition of 2 g plant stanols to cholesterol-lowering diet in a fortified yogurt in comparison with placebo in children with FH.(Jakulj et al., 2006)

- Four trials evaluated the addition of plant sterols to cholesterol-lowering diet compared with placebo in FH patients.(Amundsen et al., 2002; de Jongh et al., 2003; Fuentes et al., 2008; H. A. Neil et al., 2001) Plants sterols were administered in a fortified margarine spread at a dose ranging 1.6-2.5 g/d. Two of the trials included children with FH (Amundsen et al., 2002; de Jongh et al., 2003) and the rest studies included FH adults receiving lipid-lowering drugs(Fuentes et al., 2008; H. A. Neil et al., 2001)
- One trial compared the addition of 2 g/d plant stanols with 2 g/d plant sterols in FH adults who adhered to cholesterol-lowering diet and were on lipid-lowering therapy.(Ketomaki et al., 2005)
- Three RCTs evaluated dietary interventions modifying the protein content of the diet in FH patients.(Helk & Widhalm, 2020; Laurin et al., 1991; Wolfe & Giovannetti, 1992) Two of these trials manipulated protein content by increasing the consumption of soy protein.(Helk & Widhalm, 2020; Laurin et al., 1991) The former compared 2 different cholesterol-lowering diet with high-protein content in which 35% of the protein was consumed as dairy source, either from soy beverage or cow milk.(Laurin et al., 1991) The latter RCT investigated the addition of soy-protein to a diet high in unsaturated and low in saturated fats compared with placebo.(Helk & Widhalm, 2020) Both of these RCTs referred to children with FH. The third trial investigated the increase in protein intake on top of a cholesterol-lowering diet in FH adults.(Wolfe & Giovannetti, 1992)
- Only one trial investigated the impact of diet fibers on FH adults.(Wirth et al., 1982) In this RCT, guar gum was administered with bezafibrate and this was compared with bezafibrate given alone.(Wirth et al., 1982) The authors did not report whether their subjects adhered to cholesterol-lowering diet or not.(Wirth et al., 1982)

4.3 Bias risk within studies

A summary of the bias risk is depicted in Figure 3.

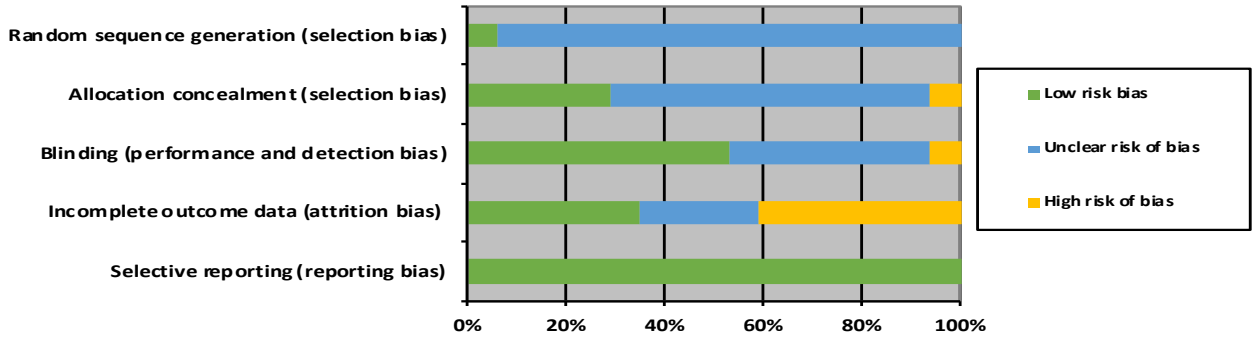


Figure 3 Bias risk graph

Judgments about each risk of bias item are presented as percentages across all included studies

Allocation

Only one trial reported adequately on the randomization sequence; they stated that computer-generated random numbers were used to assign the participants to either test or the control group with equal probability.(H. A. Neil et al., 2001) Reports on the generation of the randomization sequence were unclear in the remaining 16 trials.(Amundsen et al., 2002; Balestrieri et al., 1996; Chan et al., 2016; Chisholm et al., 1994; de Jongh et al., 2003; Fuentes et al., 2008; Gustafsson et al., 1983; Gylling et al., 1995; Hande et al., 2019; Helk & Widhalm, 2020; Jakulj et al., 2006; Ketomaki et al., 2005; Laurin et al., 1991; Negele et al., 2015; Wirth et al., 1982; Wolfe & Giovannetti, 1992)

Concealment of allocation was adequate in 5 trials where the authors have described the methods adopted for assuring allocation concealment.(de Jongh et al., 2003; Hande et al., 2019; Jakulj et al., 2006; Negele et al., 2015; H. A. Neil et al., 2001) One trial was considered to be at high bias risk due its open-label design.(Chan et al., 2016) On the other hand, data regarding allocation concealment was unclear in the rest RCTs.(Amundsen et al., 2002; Balestrieri et al., 1996; Chisholm et al., 1994; Fuentes et al., 2008; Gustafsson et al., 1983;

Gylling et al., 1995; Helk & Widhalm, 2020; Ketomaki et al., 2005; Laurin et al., 1991; Wirth et al., 1982; Wolfe & Giovannetti, 1992)

Blinding

Nine RCTs were reported as being double-blinded. (Amundsen et al., 2002; Balestrieri et al., 1996; de Jongh et al., 2003; Gylling et al., 1995; Hande et al., 2019; Jakulj et al., 2006; Ketomaki et al., 2005; Negele et al., 2015; H. A. Neil et al., 2001) One RCT was open-label (Chan et al., 2016), whereas the rest trials did not provide any information regarding blinding.(Chisholm et al., 1994; Fuentes et al., 2008; Gustafsson et al., 1983; Helk & Widhalm, 2020; Laurin et al., 1991; Wirth et al., 1982; Wolfe & Giovannetti, 1992)

Incomplete outcome data

It was unclear if an intention-to-treat analysis was carried out in one of the trials, giving thus an unclear risk of bias.(Chisholm et al., 1994) Intention-to-treat analysis was considered adequate in 6 RCTs giving a low risk of bias. (de Jongh et al., 2003; Gylling et al., 2014; Jakulj et al., 2006; Ketomaki et al., 2005; H. A. Neil et al., 2001; Wolfe & Giovannetti, 1992) In 7 RCTs participants were withdrawn and not included in the final analysis; consequently intention-to-treat analysis was not applied.(Amundsen et al., 2002; Balestrieri et al., 1996; Chan et al., 2016; Fuentes et al., 2008; Hande et al., 2019; Laurin et al., 1991; Negele et al., 2015) One trial undertook a per protocol analysis (Helk & Widhalm, 2020) and no sample attrition was performed in two RCTs.(Gustafsson et al., 1983; Wirth et al., 1982)

Selective reporting

No selective reporting was noted in the included RCTs.

4.4 Effects of interventions

Only 11 RCTs presented data in such way that the preferred method of analysis could be conducted (Amundsen et al., 2002; Balestrieri et al., 1996; Chan et al., 2016; de Jongh et al., 2003; Fuentes et al., 2008; Gylling et al., 1995; Hande et al., 2019; Helk & Widhalm, 2020; Jakulj et al., 2006; Laurin et al., 1991; H. A. Neil et al., 2001) However, these trials did not provide

data for all of the assessed outcomes. Furthermore, no RCT reported on the incidence or mortality of total CVD, CHD, stroke and PAD.

4.4.1 Dietary interventions reducing fat intake

As shown in Table 10, low-fat diet had no impact on subjects' TC (MD: -0.40 mmol/L, 95% CI: -0.95 to 0.15), TG (MD: 0.06 mmol/L, 95% CI: -0.43 to 0.55), HDL-C (MD: -0.11 mmol/L, 95% CI: -0.34 to 0.12), LDL-C (MD: -0.27 mmol/L, 95% CI: -0.79 to 0.25) and VLDL-C (MD: 0.01 mmol/L, 95% CI: -0.24 to 0.26), when compared with a higher-fat diet.(Chisholm et al., 1994)

Table 10 *Lipid profile of subjects assigned to low-fat/low-cholesterol diet and high-fat/high-cholesterol diet*

Variables/Trial	**Last visit levels**			
	High-fat diet		**Low-fat diet**	
	N	Mean (SD)	N	Mean (SD)
Chisholm 1994				
Total cholesterol, mmol/L	19	6.36 (0.98)	19	5.96 (0.75)
Triglycerides, mmol/L		1.49 (0.76)		1.55 (0.78)
High-density lipoprotein cholesterol, mmol/L		1.44 (0.38)		1.33 (0.35)
Low-density lipoprotein cholesterol, mmol/L		4.22 (0.93)		3.95 (0.70)
Very-low-density lipoprotein cholesterol, mmol/L		0.56 (0.41)		0.57 (0.37)

SD, standard deviation

4.4.2 Supplementation with omega-3 fatty acids compared with placebo

The lipid profile of subjects participating in the RCTs evaluating the administration of omega-3 fatty acids are demonstrated in Table 11.(Balestrieri et al., 1996; Chan et al., 2016; Hande et al., 2019)

According to the pooled analysis (Figure 4), the supplementation with omega-3 fatty acids decreased study participants' TG (MD: -0.27 mmol/L, 95% CI: -0.47 to -0.07, p <0.01), but had no impact on their HDL-C (MD: -0.02 mmol/L, 95% CI: -0.16 to 0.12) and apoB100 (MD: -0.06 g/L, 95% CI: -0.18 to 0.06). A non-significant trend towards a reduction in subjects' TC (MD: -0.34 mmol/L, 95% CI: -0.68 to 0, p=0.05) and LDL-C (MD: -0.31 mmol/L, 95% CI: -0.61 to 0,

p=0.05) was noticed (Figure 4). No significant heterogeneity was noticed across studies (Figure 4).

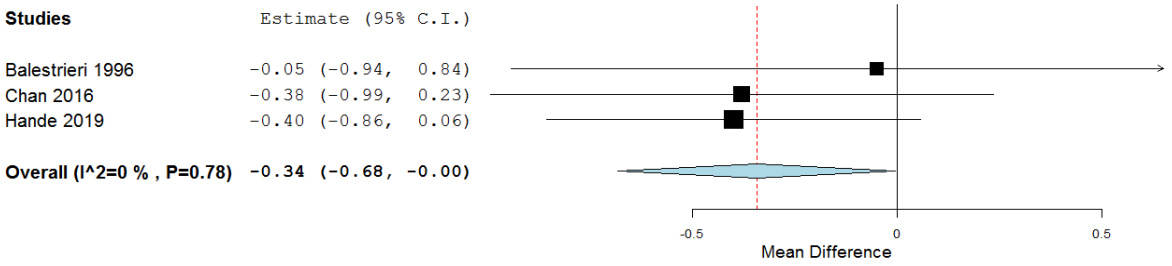
As shown in Table 11, individual studies showed that omega-3 fatty acids decreased subjects' VLDL-C (MD: -0.20 mmol/L, 95% CI: -0.23 to -0.16, p <0.05) (Chan et al., 2016), but no effect was noticed regarding their apoA-I (MD: 0.02 g/L, 95% CI: -0.31 to 0.35) and Lp(a) (MD: -0.02 g/L, 95% CI:-0.31 to 0.27).(Balestrieri et al., 1996)

Table 11 *Lipid profile of subjects assigned to omega-3 fatty acids and placebo*

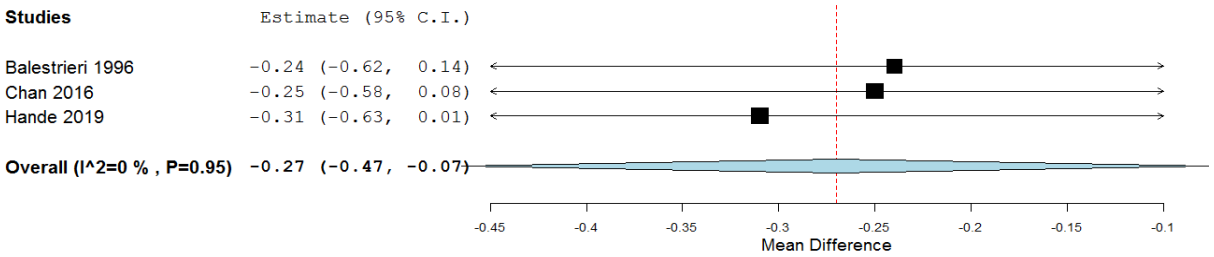
Variables/Trial	**Last visit levels**			
	Omega-3 fatty acids group		**Placebo group**	
	N	Mean (SD)	N	Mean (SD)
Balestrieri 1996	14		14	
Total cholesterol, mmol/L		7.75 (1.27)		7.80 (1.14)
Triglycerides, mmol/L		1.02 (0.29)		1.26 (0.66)
High-density lipoprotein cholesterol, mmol/L		1.37 (0.54)		1.34 (0.47)
Low-density lipoprotein cholesterol, mmol/L		5.89 (1.29)		5.87 (1.34)
Apolipoprotein A-I, g/L		1.27 (0.47)		1.25 (0.42)
Apolipoprotein B100, g/L		2.04 (0.42)		2.05 (0.42)
Chan 2016	20		20	
Total cholesterol, mmol/L		4.20 (0.71)		4.58 (1.21)
Triglycerides, mmol/L		1.05 (0.40)		1.30 (0.63)
High-density lipoprotein cholesterol, mmol/L		1.12 (0.22)		1.19 (0.54)
Low-density lipoprotein cholesterol, mmol/L		2.54 (0.71)		2.81 (0.85)
Very-low-density lipoprotein cholesterol, mmol/L		0.57 (0.22)		0.77 (0.28)
Apolipoprotein B100, g/L		0.76 (0.13)		0.83 (0.27)
Lipoprotein (a), g/L		0.42 (0.45)		0.44 (0.49)
Hande 2019	34		34	
Total cholesterol, mmol/L		4.60 (0.80)		5.00 (1.10)
Triglycerides, mmol/L		0.84 (0.39)		1.15 (0.86)
High-density lipoprotein cholesterol, mmol/L		1.4 (0.4)		1.4 (0.4)
Low-density lipoprotein cholesterol, mmol/L		2.8 (0.9)		3.2 (0.9)

SD, standard deviation

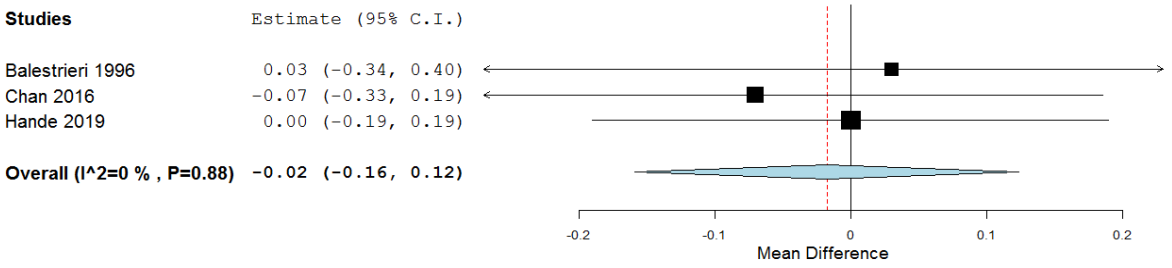
Total cholesterol



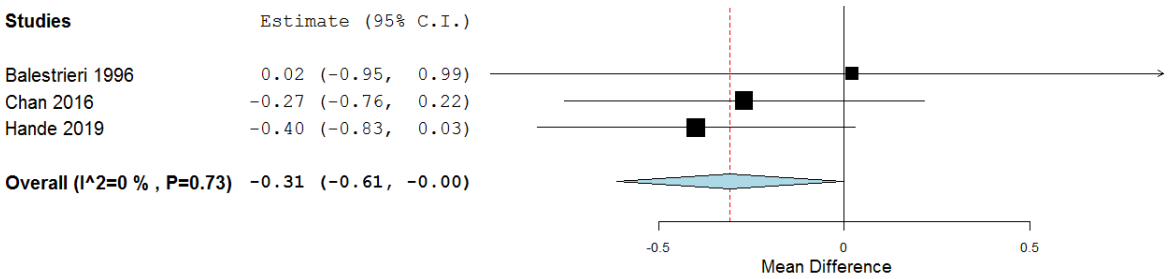
Triglycerides



High-density lipoprotein cholesterol



Low-density lipoprotein cholesterol



Apolipoprotein B100

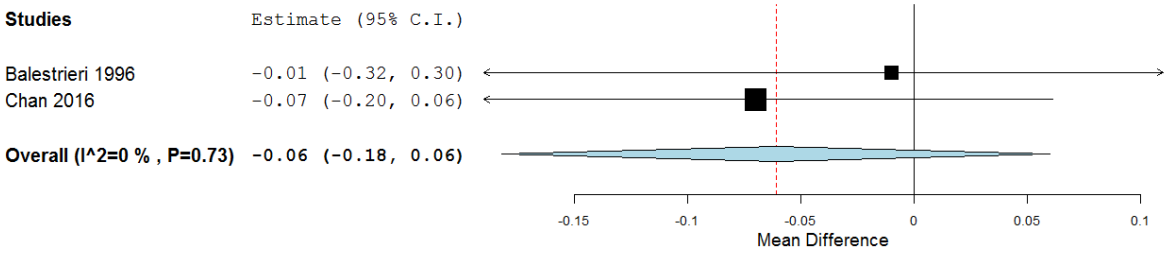


Figure 4 Effect of supplementation with omega-3 fatty acids compared with placebo

4.4.3 Dietary interventions modifying unsaturated fat content

Low-fat diet regimes enriched with either monounsaturated fatty acids or polyunsaturated fatty acids

As shown in Table 12, the trial comparing two low-fat diet regimes enriched with either MUFAs or PUFAs showed no difference between 2 groups regarding subjects' TC (MD: -0.73 mmol/L, 95% CI: -1.69 to 0.23), TG (MD: -0.03 mmol/L, 95% CI: -0.53 to 0.47), HDL-C (MD: 0.10 mmol/L, 95% CI: -0.19 to 0.39), LDL-C (MD: -0.84 mmol/L, 95% CI: -1.90 to -0.22), apoA-I (MD: -0.01 g/L, 95% CI: -0.25 to 0.23) and apoB100 (MD: -0.09 g/L, 95% CI: -0.36 to 0.18).(Negele et al., 2015)

Table 12 *Lipid profile of subjects assigned to low-fat diet regimes enriched with either monounsaturated fatty acids or polyunsaturated fatty acids*

Variables/Trial	Last visit levels			
	Monounsaturated fat		**Polyunsaturated fat**	
	N	Mean (SD)	N	Mean (SD)
Negele 2015	12		9	
Total cholesterol, mmol/L		5.55 (0.75)		6.28 (1.32)
Triglycerides, mmol/L		1.11 (0.63)		1.14 (0.54)
High-density lipoprotein cholesterol, mmol/L		1.57 (0.24)		1.47 (0.39)
Low-density lipoprotein cholesterol, mmol/L		3.46 (0.55)		4.30 (1.55)
Apolipoprotein A-I, g/L		1.40 (0.23)		1.41 (0.31)
Apolipoprotein B100, g/L		1.08 (0.32)		1.17 (0.30)

SD, standard deviation

Cholesterol-lowering diets differing with regard to polyunsaturated:saturated values

One study showed that that increasing the PUFAs:saturated fat value of lipid-lowering diets from 1.3 to 2.0 did not offer a great advantage with regard to reduction in subjects' TC (0.03 ± 0.64 mmol/L), TG (-0.01 ± 0.23 mmol/L), HDL-C (0 ± 0.13 mmol/L), LDL-C (0.02 ± 0.06 mmol/L) and VLDL-C (0.09 ± 0.13 mmol/L).(Gustafsson et al., 1983)

4.4.4 Cholesterol-lowering diet compared with dietary interventions increasing intake of plant stanols

The lipid profile of subjects participating in the RCTs evaluating the dietary interventions increasing the intake of plant stanols are demonstrated in Table 13.(Gylling et al., 1995; Jakulj et al., 2006)

According to the pooled analysis (Figure 5), the increased intake of plant stanols reduced study participants' TC (MD: -0.62 mmol/L, 95% CI: -1.13 to -0.11, p=0.02) and LDL-C (MD: -0.58 mmol/L, 95% CI: -1.08 to -0.09, p=0.02), but they had no impact on their TG (MD: -0.02 mmol/L, 95% CI: -0.09 to 0.14) and HDL-C (MD: -0.01 mmol/L, 95% CI: -0.11 to 0.09). No significant heterogeneity was noticed across studies (Figure 5).

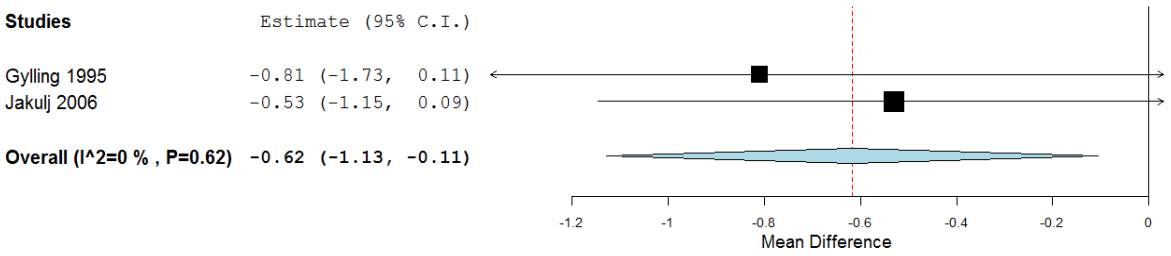
As shown in Table 13, one study showed that plant stanols had no impact on subjects' VLDL-C (MD: -0.08 mmol/L, 95% CI: -0.26 to 0.10).(Gylling et al., 1995)

Table 13 *Lipid profile of subjects assigned to plant stanols and placebo*

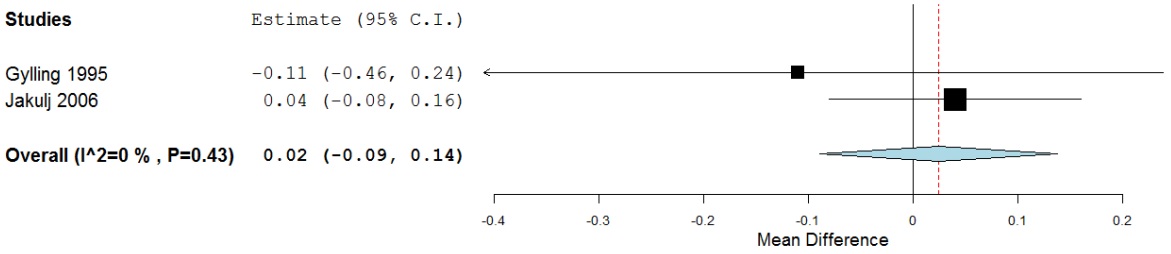
Variables/Trial	**Last visit levels**			
	Plant stanols group		**Placebo group**	
	N	Mean (SD)	N	Mean (SD)
Gylling 1995	14		14	
Total cholesterol, mmol/L		6.81 (1.27)		7.62 (1.20)
Triglycerides, mmol/L		0.92 (0.45)		1.03 (0.49)
High-density lipoprotein cholesterol, mmol/L		1.25 (0.30)		1.20 (0.26)
Low-density lipoprotein cholesterol, mmol/L		4.65 (1.20)		5.47 (1.12)
Very-low-density lipoprotein cholesterol, mmol/L		0.25 (0.26)		0.26 (0.22)
Jakulj 2006	41		41	
Total cholesterol, mmol/L		6.47 (1.35)		7.00 (1.49)
Triglycerides, mmol/L		0.61 (0.24)		0.57 (0.31)
High-density lipoprotein cholesterol, mmol/L		1.35 (0.24)		1.38 (0.27)
Low-density lipoprotein cholesterol, mmol/L		4.77 (1.32)		5.24 (1.45)

SD, standard deviation

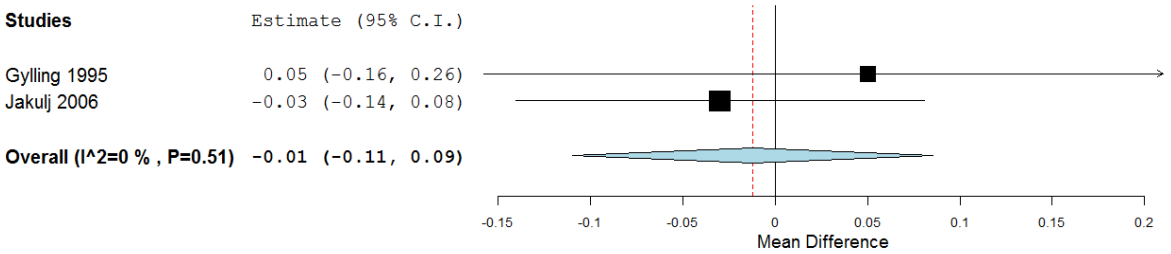
Total cholesterol



Triglycerides



High-density lipoprotein cholesterol



Low-density lipoprotein cholesterol

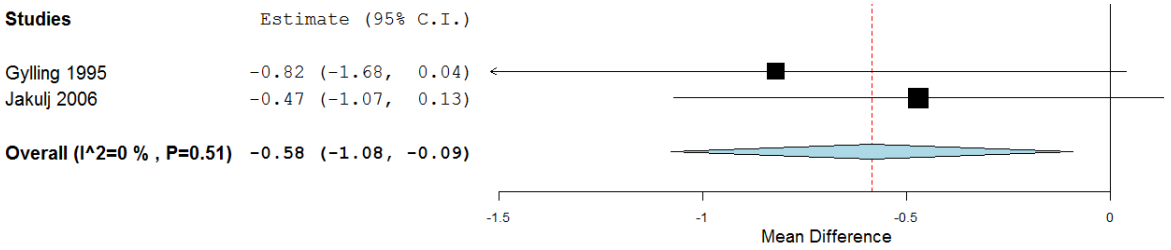


Figure 5 Effect of increased intake of plant stanols compared with placebo

4.4.5 Cholesterol-lowering diet compared with dietary interventions increasing intake of plant sterols

The lipid profile of subjects participating in the RCTs evaluating the dietary interventions increasing the intake of plant sterols are demonstrated in Table 14.(Amundsen et al., 2002; de Jongh et al., 2003; Fuentes et al., 2008; H. A. Neil et al., 2001)

Table 14 *Lipid profile of subjects assigned to plant sterols and placebo*

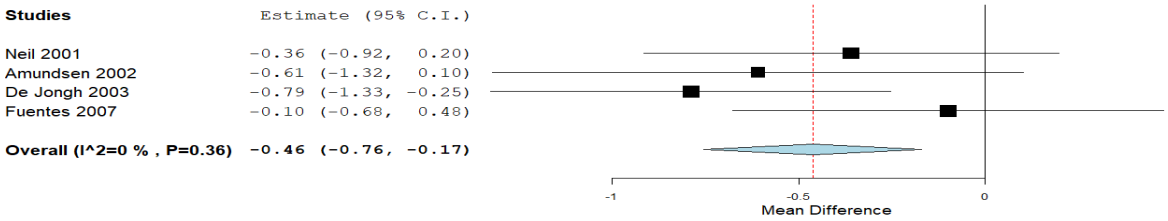
Variables/Trial	Last visit levels			
	Plant sterols group		Placebo group	
	N	Mean (SD)	N	Mean (SD)
Neil 2001	29		29	
Total cholesterol, mmol/L		6.84 (1.12)		7.20 (1.04)
Triglycerides, mmol/L		1.27 (0.65-3.80)		1.29 (0.66-3.93)
High-density lipoprotein cholesterol, mmol/L		1.49 (0.36)		1.43 (0.36)
Low-density lipoprotein cholesterol, mmol/L		4.65 (1.14)		4.99 (1.02)
Very-low-density lipoprotein cholesterol, mmol/L		0.73 (0.30)		0.81 (0.38)
Apolipoprotein A-I, g/L		1.41 (0.25)		1.47 (0.26)
Apolipoprotein B, g/L		1.46 (0.33)		1.47 (0.29)
Amundsen 2002	38		38	
Total cholesterol, mmol/L		6.87 (1.45)		7.48 (1.70)
Triglycerides, mmol/L		0.80 (0.37)		0.78 (0.33)
High-density lipoprotein cholesterol, mmol/L		1.26 (0.35)		1.25 (0.31)
Low-density lipoprotein cholesterol, mmol/L		5.25 (1.55)		5.88 (1.79)
Apolipoprotein A-I, g/L		1.32 (0.26)		1.35 (0.23)
Apolipoprotein B, g/L		1.32 (0.35)		1.48 (0.39)
De Jongh 2003	41		41	
Total cholesterol, mmol/L		6.27 (1.12)		7.06 (1.35)
Triglycerides, mmol/L		0.85 (0.36)		0.90 (0.40)
High-density lipoprotein cholesterol, mmol/L		1.31 (0.31)		1.29 (0.29)
Low-density lipoprotein cholesterol, mmol/L		4.58 (1.13)		5.40 (1.37)
Fuentes 2007	30		30	
Total cholesterol, mmol/L		5.74 (1.03)		5.84 (1.24)
Triglycerides, mmol/L		1.08 (0.61)		1.14 (0.49)
High-density lipoprotein cholesterol, mmol/L		1.39 (0.36)		1.37 (0.36)
Low-density lipoprotein cholesterol, mmol/L		3.83 (0.96)		3.96 (1.09)
Apolipoprotein A-I, g/L		1.46 (0.22)		1.47 (0.26)
Apolipoprotein B, g/L		1.11 (0.21)		1.14 (0.24)

SD, standard deviation

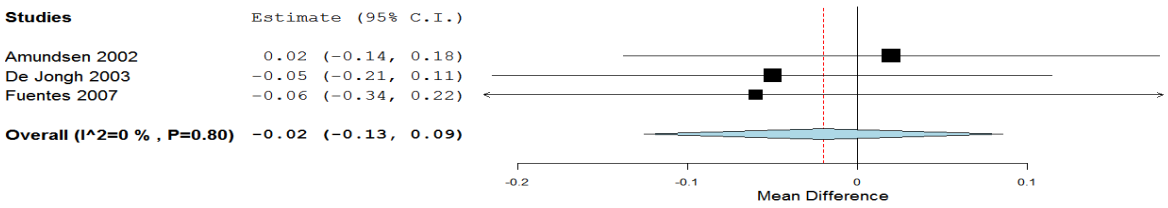
According to the pooled analysis (Figure 6), the increased intake of plant stanols reduced study participants' TC (MD: -0.46 mmol/L, 95% CI: -0.76 to -0.17, p <0.01) and LDL-C (MD: -0.45 mmol/L, 95% CI: -0.74 to -0.16, p <0.01). On the other hand, no effect was noticed regarding their TG (MD: -0.02 mmol/L, 95% CI: -0.13 to 0.09), HDL-C (MD: 0.02 mmol/L, 95% CI: -0.05 to 0.1,), apoA-I (MD: -0.03 g/L, 95% CI: -0.10 to 0.04) and apoB (MD: -0.06 g/L, 95% CI: -0.14 to 0.03). No significant heterogeneity was noticed across studies (Figure 6).

One study showed no impact on VLDL-C (MD: -0.08 mmol/L, 95% CI: -0.26 to 0.10).(H. A. Neil et al., 2001)

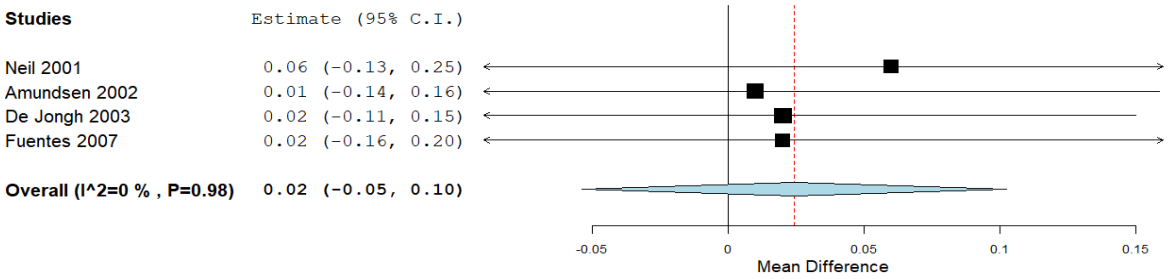
Total cholesterol



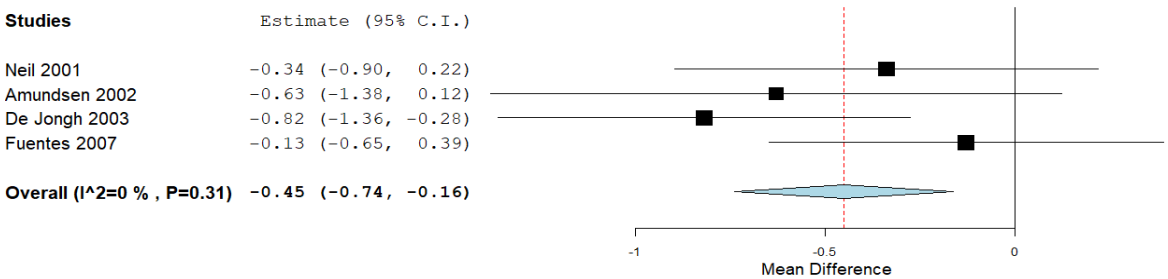
Triglycerides



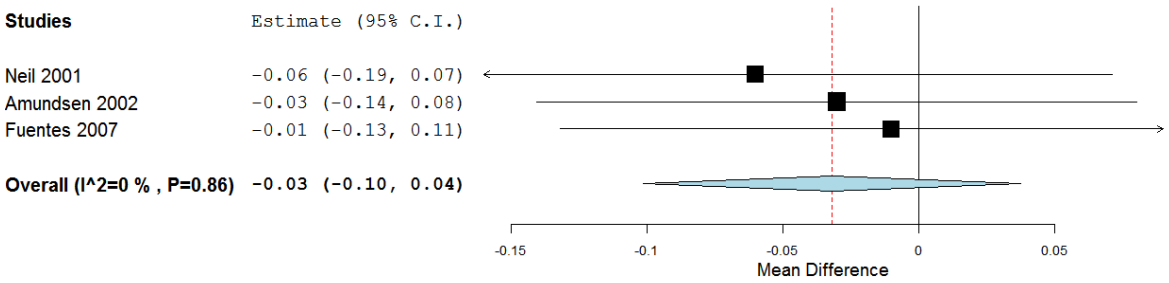
High-density lipoprotein cholesterol



Low-density lipoprotein cholesterol



Apolipoprotein A-I



Apolipoprotein B

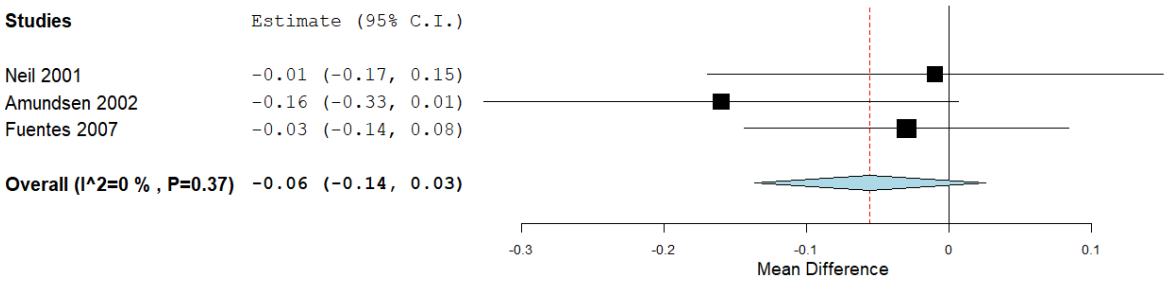


Figure 6 Effect of increased intake of plant sterols compared with placebo

4.4.6 Dietary interventions increasing intake of plant stanols compared with plant sterols

As shown in Table 15, there was no difference between the addition of 2 g/d plant stanols and 2 g/d plant sterols in FH adults who adhered to cholesterol-lowering diet regarding their TC (MD: -0.06 mmol/L, 95% CI: -0.66 to 0.54), TG (MD: 0.11 mmol/L, 95% CI: -0.18 to 0.40), HDL-C (MD: -0.05 mmol/L, 95% CI: -0.16 to 0.06) and LDL-C (MD: -0.05 mmol/L, 95% CI: -0.56 to 0.46).(Ketomaki et al., 2005)

Table 15 *Lipid profile of subjects assigned to plant stanols and plant sterols*

Variables/Trial	Last visit levels			
	Stanols group		Sterols group	
	N	Mean (SD)	N	Mean (SD)
Ketomaki 2005	18		18	
Total cholesterol, mmol/L		5.65 (0.93)		5.71 (0.89)
Triglycerides, mmol/L		1.16 (0.51)		1.05 (0.38)
High-density lipoprotein cholesterol, mmol/L		1.32 (0.17)		1.37 (0.17)
Low-density lipoprotein cholesterol, mmol/L		3.81 (0.76)		3.86 (0.81)

SD, standard deviation

4.4.7 Dietary interventions modifying protein content

Soy protein as a form of dietary intervention compared to another form or no intervention

The lipid profile of subjects participating in the RCTs evaluating the dietary interventions increasing soy protein intake is demonstrated in Table 16.(Helk & Widhalm, 2020; Laurin et al., 1991)

According to the pooled analysis (Figure 7), the dietary interventions increasing soy intake had no impact on study participants' TC (MD: -0.19 mmol/L, 95% CI: -0.78 to 0.41), TG (MD: -0.14 mmol/L, 95% CI: -0.30 to 0.02), HDL-C (MD: 0.08 mmol/L, 95% CI: -0.06 to 0.22L), LDL-C (MD: -0.41 mmol/L, 95% CI: -0.99 to 0.18), VLDL-C (MD: -0.06 mmol/L, 95% CI: -0.13 to 0.01), apoA-I (MD: -0.02 g/L, 95% CI: -0.10 to 0.05) and apoB (MD: -0.04 g/L, 95% CI: -0.14 to 0.06). No significant heterogeneity was noticed across studies, apart from the analysis concerning LDL-C (Figure 7).

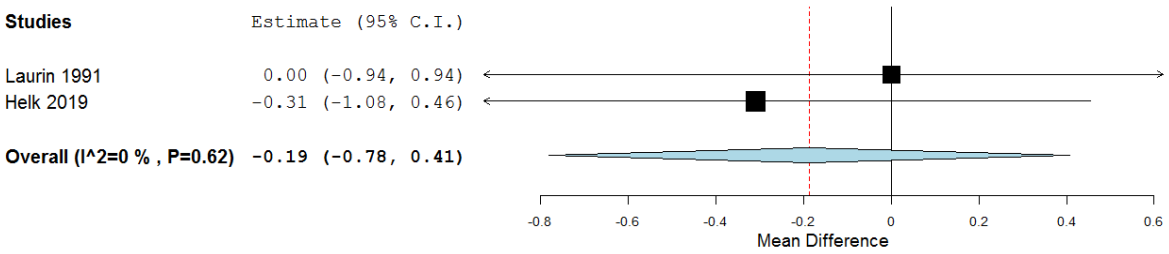
As shown in Table 16, one study showed that soy had no impact on subjects' Lp(a) (MD: -0.29 g/L, 95% CI: -0.65 to 0.07).(Helk & Widhalm, 2020)

Table 16 *Lipid profile of subjects assigned to soy protein and control group*

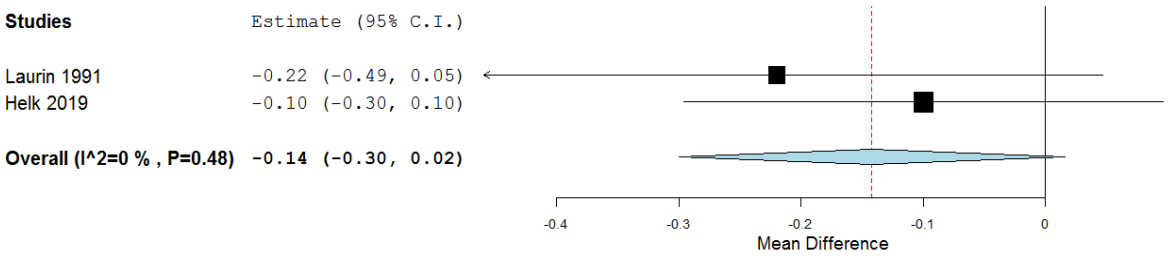
Variables/Trial	**Last visit levels**			
	Soy group		**Control group**	
	N	Mean (SD)	N	Mean (SD)
Laurin 1991	9		9	
Total cholesterol, mmol/L		7.89 (1.02)		7.89 (1.02)
Triglycerides, mmol/L		0.80 (0.24)	`	1.02 (0.33)
High-density lipoprotein cholesterol, mmol/L		1.20 (0.21)		1.15 (0.18)
Low-density lipoprotein cholesterol, mmol/L		6.33 (1.02)		6.29 (1.11)
Very-low-density lipoprotein cholesterol, mmol/L		0.35 (0.12)		0.45 (0.15)
Apolipoprotein A-I, g/L		1.55 (0.09)		1.59 (0.15)
Apolipoprotein B, g/L		1.44 (0.06)		1.44 (0.18)
Helk 2019	13		13	
Total cholesterol, mmol/L		6.27 (0.96)		6.58 (1.03)
Triglycerides, mmol/L		71.9(23.40)		80 (16.7)
High-density lipoprotein cholesterol, mmol/L		1.63 (0.26)		1.51 (12.6)
Low-density lipoprotein cholesterol, mmol/L		4.00 (0.78)		4.65 (1.08)
Very-low-density lipoprotein cholesterol, mmol/L		0.37 (0.12)		0.41 (0.09)
Apolipoprotein A-I, g/L		1.36 (0.13)		1.37 (0.15)
Apolipoprotein B, g/L		1.13 (0.19)		1.23 (0.21)
Lipoprotein (a), g/L		0.30 (0.29)		0.59 (0.59)

SD, standard deviation

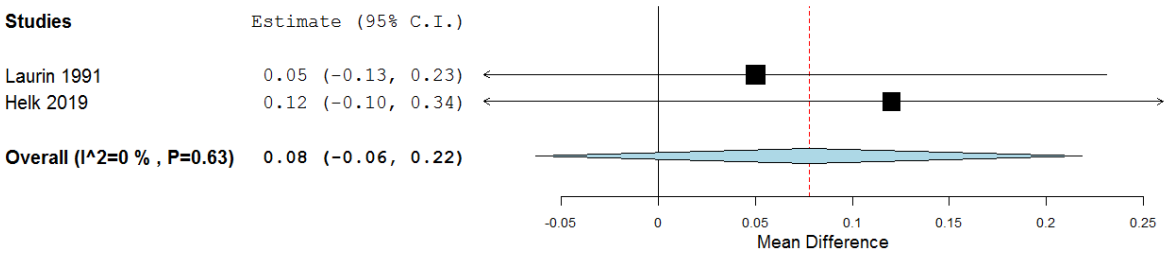
Total cholesterol



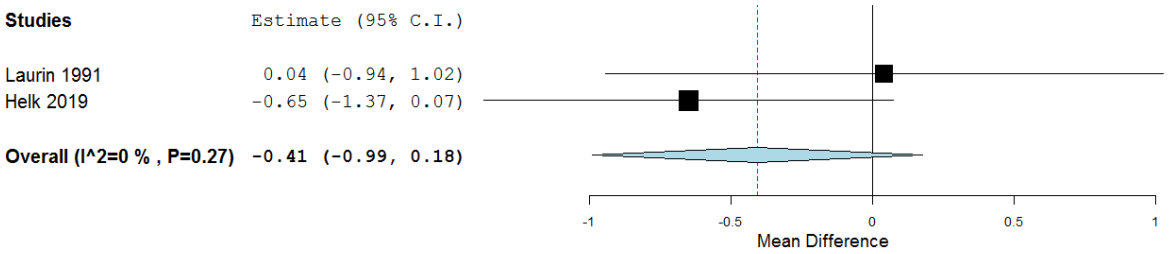
Triglycerides



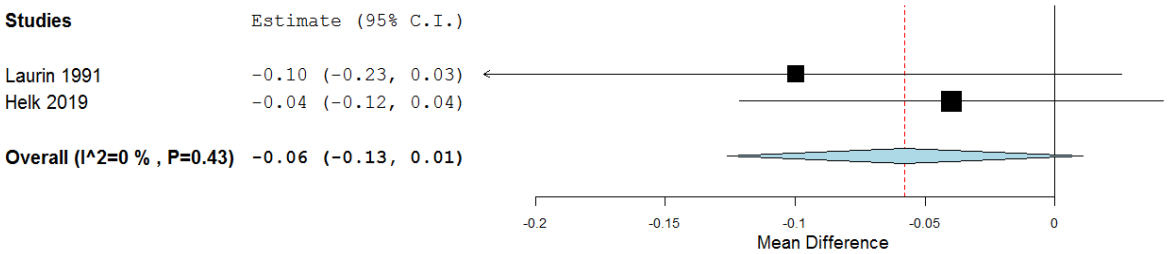
High-density lipoprotein cholesterol



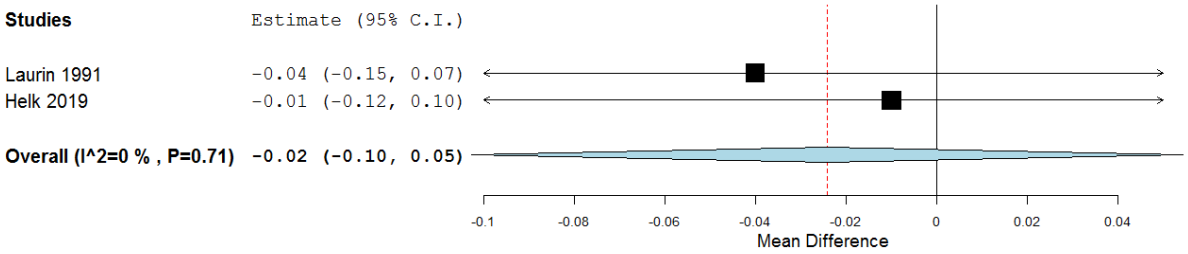
Low-density lipoprotein cholesterol



Very-low-density lipoprotein cholesterol



Apolipoprotein A-I



Apolipoprotein B

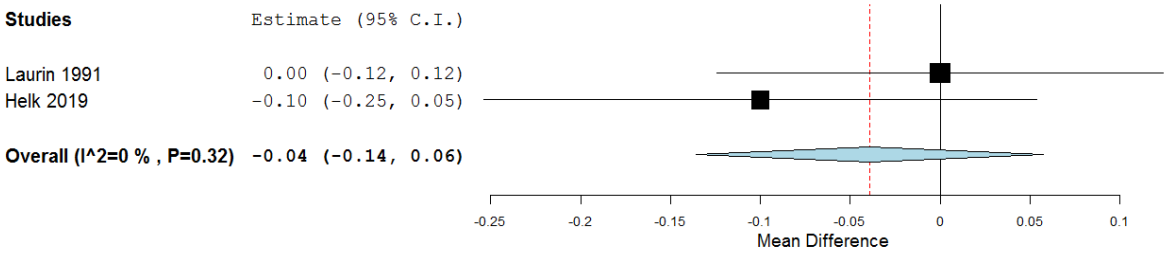


Figure 7 Effect of increased intake of soy protein compared with control group

Dietary intervention to increase protein intake

As shown in Table 17, the dietary interventions increasing protein intake reduced subjects' TG (MD: -0.70 mmol/L, 95% CI: -1.32 to -0.08, p <0.05) and LDL-C (MD: -0.30 mmol/L, 95% CI: -0.85 to -0.25, p <0.05), but had no impact on their TC (MD: -0.40 mmol/L, 95% CI: -1.23 to 0.43), VLDL-C (MD: -0.17 mmol/L, 95% CI: -0.44 to 0.10) and HDL-C (MD: 0.08 mmol/L, 95% CI: -0.14 to 0.10).(Wolfe & Giovannetti, 1992)

Table 17 *Lipid profile of subjects assigned to increased and low protein intake*

	Last visit levels			
	High-protein group		Low-protein group	
	N	Mean (SD)	N	Mean (SD)
Wolfe 1992	10		10	
Total cholesterol, mmol/L		5.7 (0.95)		6.1 (0.95)
Triglycerides, mmol/L		1.7 (0.32)		2.4 (0.95)
High-density lipoprotein cholesterol, mmol/L		0.97 (0.25)		0.89 (0.25)
Low-density lipoprotein cholesterol, mmol/L		4.5 (0.63)		4.8 (0.63)
Very-low-density lipoprotein cholesterol, mmol/L		0.49 (0.25)		0.66 (0.35)

SD, standard deviation

4.4.8 Dietary interventions to increase intake of dietary fiber

As shown in Table 18, the dietary interventions increasing dietary fiber intake decreased subjects' LDL-C (MD: -1.83 mmol/L, 95% CI: -3.32 to -0.34, p <0.05) and apoB (MD: -0.50 g/L, 95% CI: -0.65 to -0.35, p <0.05). On the other hand, guar had no impact on their TC (MD: -0.57 mmol/L, 95% CI: -2.08 to 0.94), TG (MD: 0.41 mmol/L, 95% CI: -0.12 to 0.94), HDL-C (MD: -0.18 mmol/L, 95% CI: -0.47 to 0.11) and apoA-I (MD: 0.04 g/L, 95% CI: -0.05 to 0.13).(Wirth et al., 1982)

Table 18 *Lipid profile of subjects assigned to bezafibrate plus guar and bezafibrate alone*

Variables/Trial	**Last visit levels**			
	Intervention group		Placebo group	
	N	Mean (SD)	N	Mean (SD)
Wirth 1982	12		12	
Total cholesterol, mmol/L		8.52 (1.78)		9.09 (1.99)
Triglycerides, mmol/L		1.87 (0.49)		1.46 (0.79)
High-density lipoprotein cholesterol, mmol/L		1.24 (0.33)		1.42 (0.38)
Low-density lipoprotein cholesterol, mmol/L		6.08 (1.91)		7.91 (1.81)
Apolipoprotein A-I, g/L		1.21 (0.1)		1.17 (0.12)
Apolipoprotein B, g/L		1.55 (0.17)		2.05 (0.21)

SD, standard deviation

CHAPTER 5 DISCUSSION

The present meta-analysis included 17 RCTs evaluating the impact of different dietary interventions on lipid levels of children and adults diagnosed with FH. No RCT investigating the impact of dietary interventions on CVD incidence or mortality was found. According to our pooled analyses, increased intake of plants sterols and stanols by fortified foods reduce TC and LDL-C in such individuals. Although a non-significant trend towards a reduction in TC and LDL-C was noticed, supplementation with omega-3 fatty acids resulted in TG decrease in this population.

FH is the most commonly inherited metabolic disease and associated with premature CVD, if left untreated.(Austin et al., 2004a; F. Barkas et al., 2016; Goldberg et al., 2011; Hutter et al., 2004; Raal et al., 2018) Considering LDL-C reduction (over 50%) needed for the prevention against CVD development in FH patients, lipid-lowering drugs are the primary CV prevention therapy in such individuals.(Goldberg et al., 2011; Mach et al., 2020; Raal et al., 2018) Statins and ezetimibe remain the cornerstone treatment, whereas PCSK9 inhibitors, mipomersen and lopitamide have been approved for FH patients not achieving optimal LDL-C levels.(F Barkas et

al., 2018; Goldberg et al., 2011; Mach et al., 2020; Raal et al., 2018) Novel lipid-lowering drugs, such as inclisiran, angiopoietin-like 3 protein, bempedoic acid and gemcabene are a few therapeutic options currently investigated for the future management of such individuals.(Raal et al., 2018) Despite the available effective lipid-lowering drugs, a considerable proportion of patients diagnosed with FH remain suboptimally treated in clinical practice.(F. Barkas et al., 2016; Nordestgaard, 2016) In addition, a considerable proportion of patients diagnosed with FH cannot be treated with lipid-lowering drugs, such as statin-intolerant and pregnant patients or children aged <8 years old.(Mach et al., 2020) In this context, dietary interventions including diet modification or dietary supplements might be helpful if not necessary in FH individuals. Although current guidelines propose manipulating dietary fat, increasing fiber intake or certain dietary components (Mach et al., 2020), the majority of these interventions have not been adequately investigated in patients with FH.

Although cholesterol-lowering diet is the primary dietary suggestion in patients diagnosed with FH, only one study including FH adults has compared low-fat/low-cholesterol diet with a diet of higher content in fat and cholesterol and showed no difference between 2 interventions.(Chisholm et al., 1994) However, it has to be noticed that no data were available regarding the fat quality in subjects' diet.(Chisholm et al., 1994) Therefore, considering the fact that reduction of total fat intake is not so important as the modification of fat quality (ie. replacement of dietary trans fatty acids with PUFAs) in CV prevention and cholesterol reduction (Judd et al., 1994; Lichtenstein et al., 1999), the results of Chisholm et al. are insufficient to reach any conclusion on the efficacy of cholesterol-lowering diet in FH patients.

Similar to previous meta-analyses including dyslipidemic patients not fulfilling the criteria for FH (Mozaffarian & Wu, 2011), ours demonstrated that supplementation with omega-3 fatty acids significantly reduce TG, but has no impact on HDL-C levels of FH individuals. On the other hand, our results showing a non-significant trend towards a reduction in TC and LDL-C support the conflicting evidence regarding the impact of omega-3 fatty acids on cholesterol.(Mozaffarian & Wu, 2011; Pan et al., 2009; Ursoniu et al., 2017) In this context, additional studies are needed to evaluate different quantity of EPA/DHEA or quality of omega-3 fatty acids on FH patients' cholesterol indices. Indeed, REDUCE-IT trial which assigned its subjects to

icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester or placebo, showed that the former was associated with a significant non-HDL-C and apoB reduction.(Bhatt et al., 2019)

One trial comparing 2 cholesterol-lowering diets enriched with either MUFAs or PUFAs in FH patients did not confirm available evidence supporting that PUFAs may have a greater impact on LDL-C reduction than MUFAs.(Astrup et al., 2011; Negele et al., 2015) Similarly, the replacement of saturated fat with PUFAs had no impact on FH patients' lipid profile in another study.(Gustafsson et al., 1983) Nevertheless, the controversial results of these studies should be taken into account after considering the lack of data on their subjects' fat quality and the limitations regarding their small sample and design.

Undoubtedly, plant sterols and stanols are effective lipid-lowering dietary interventions and suggested by current guidelines for the management of dyslipidemias.(Demonty et al., 2009; Ras et al., 2014; Rideout et al., 2009) Not only our results confirmed previous evidence, but also showed that the cholesterol-lowering benefit of phytosterols seems greater in FH individuals; the average LDL-C reduction was 0.45-0.58 mmol/L in our analyses, whereas the corresponding reduction was 0.34 mmol/L in another one including RCTs with dyslipidemic individuals.(Demonty et al., 2009) On the other hand, our results did not confirm available evidence supporting that phytosterols may also lower TG in normotriglyceridemic individuals.(Ras et al., 2014; Rideout et al., 2009)
Only one study has performed head-to-head comparisons between phytosterols in FH patients and showed no difference between 2 groups.(Ketomaki et al., 2005) According to our results, a greater LDL-C reduction was noticed in the case of plant stanols rather than plant sterols (0.58 vs 0.45 mmol/L). Despite not being significant, a similar trend was demonstrated by another meta-analysis including studies with hypercholesterolemic patients (MD: -0.13 mmol/L, 95% CI: -0.38 to 0.12, for the comparison between plant stanols and sterols).(Demonty et al., 2009)

Our pooled analysis of 2 RCTs did not confirm the beneficial effect of increased soy consumption on cholesterol reduction.(D. J. A. Jenkins et al., 2019) However, it has to be noticed that apart from the limited number of the included RCTs in the analysis and their small sample, their control groups differed. The former compared 2 cholesterol-lowering/high-

protein diets with increased intake of either soy protein or cow milk (Laurin et al., 1991) and the latter compared a soy-enriched fat modified diet with a fat modified diet.(Helk & Widhalm, 2020) On the other hand, a small RCT demonstrated that increased protein intake decreased FH patients' LDL-C and TG.(Wolfe & Giovannetti, 1992) Of note, no data were available regarding subjects' protein food sources. Therefore, future studies are needed in order to confirm the cholesterol-lowering effect of increased intake of soy protein in individuals diagnosed with FH.

Finally, the only RCT evaluating the impact of increased guar intake in FH patients has confirmed available evidence supporting the beneficial effect of dietary fiber on lipids.(Brown et al., 1999; Jovanovski et al., 2018)

Our results should be considered under certain limitations. First, only a few RCTs have investigated the impact of dietary interventions in patients with FH. Not only their samples were small, but also, they were short-term. In addition, the criteria for FH diagnosis was not defined in all studies and only almost half RCTs included patients taking lipid-lowering therapy. Finally, publication bias cannot be ruled out. As shown in Figure 3, there was no adequate data to assess selection, performance and detecting bias. However, a high-risk attrition bias was noticed. On the other hand, the present meta-analysis is the most recent to amplify the limited bibliography reporting on the impact of diet on FH patients. Malhotra et al were the last to perform a similar meta-analysis to ours in 2014 and confirm only the lipid-lowering effect of plant sterols on FH individuals.(Malhotra et al., 2014) In contrast to them, we included 7 additional RCTs in the present meta-analysis. Of note, a few methodologic issues should be considered in the previous meta-analysis by Malhotra et al. Two RCTs included in their pooled analyses did not report separately on the subgroup of FH patients.(Engler et al., 2004; Nigon et al., 2001) In addition, their pooled analysis evaluating the dietary interventions increasing the intake of plant stanols included 2 RCTs; the former assigned their participants to plant stanols and placebo, but the latter assigned their subjects to plant stanols and plant sterols.(Gylling et al., 1995; Ketomaki, Gylling, & Miettinen, 2004) Finally, their pooled analysis evaluating protein intake included 2 trials with different dietary interventions. As already mentioned, Laurin et al. compared 2 low-fat/high-protein diets enriched by either soy protein or cow milk and Wolfe et

al. compared a high- with a low-protein diet.(Laurin et al., 1991; Wolfe & Giovannetti, 1992) Therefore, our meta-analysis provides valuable data regarding the role of dietary interventions in CV prevention in FH patients. The addition of plant sterols and stanols to cholesterol-lowering diet, along with omega-3 fatty acids supplementation undoubtedly reduce cholesterol and TG in such individuals. However, future trials are needed to confirm the benefit of cholesterol-lowering diet and soy intake in this population. Last but not least, long RCTs could also elucidate the impact of such interventions on CVD incidence and mortality.

CHAPTER 6 CONCLUSIONS

No robust conclusions can be reached about the impact of a cholesterol-lowering diet or any of the other dietary interventions proposed for FH patients on CVD incidence or mortality. Available RCTs confirm that the addition of plant sterols or stanols to low-fat diet has a cholesterol-lowering effect on such individuals. On the other hand, supplementation with omega-3 fatty acids effectively reduce TG and might have a role in further lowering cholesterol of patients with FH. Additional RCTs are needed to investigate the effectiveness of cholesterol-lowering diet and the addition of soya protein and dietary fibers to a cholesterol-lowering diet in patients with FH.

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APPENDIX

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	13-16
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	68-69
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	69
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	71-72
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	72
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	72
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	72
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	72-73

Section/topic	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	74
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	74-75
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	74-75
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	74-75
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	74-75
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	75
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	76
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	77-80
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	81-82
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	82-95
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	82-95
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	82-95
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	82-95

Section/topic	#	Checklist item	Reported on page #
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	96-99
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	99-100
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	101
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

N/A, Not applicable