UNIVERSITY OF BIRMINGHAM

NHS Health Check evidence review to support content review process

Report

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1. Executive Summary

Background

NHS Health Checks are offered to all individuals aged 40 to 74 not currently on a chronic disease register. All those who attend undergo assessment including a cholesterol test (total cholesterol, LDL and HDL cholesterol levels). In addition to lifestyle advice, those at ≥10% ten-year cardiovascular disease (CVD) risk are eligible for treatment with statins and those with blood pressure ≥160/100 mm Hg or with blood pressure ≥140/90 mm Hg and ten-year CVD risk ≥20% are eligible for antihypertensive treatment. A policy of selective cholesterol testing has been proposed. Cholesterol testing would be restricted to selected patients whose ten-year CVD risk is estimated (based on available risk factors) to be above 10%.

This raises two broad questions. What proportion of individuals eligible for preventive drugs would be missed under a policy of selective cholesterol testing? What effect would selective testing have on uptake of (attendance at) NHS Health Checks?

Rapid review of the evidence

A rapid review was undertaken to identify studies which might answer these questions. Bibliographic databases were searched to April 2018 and grey literature was sought. The main literature search identified 2,502 records. After screening, 99 full texts were selected as potentially relevant. The main search was supplemented with additional searches to capture qualitative studies on health checks and cholesterol testing which identified 588 and 652 records respectively and further 46 full texts were selected as potentially relevant. No studies could directly answer any of the questions. However, a small number of studies and one PhD thesis provided some relevant information.

Findings

No analysis made use of the QRisk equations which are currently in use in the UK. One study calculated a measure of discrimination (Area Under the Curve: AUC) for Framingham and PROCAM CVD risk scores calculated using an estimated average cholesterol level and using measured cholesterol levels. The use of average values rather than measured values had no effect on AUC and resulted in fewer false positive results. Another found age to be a much more important determinant of risk using the ASCVD equation than cholesterol levels. A secondary analysis was conducted of Health Survey for England data, using a method undertaken in a PhD thesis (author TM). This demonstrated that undertaking cholesterol testing in 53% of the population identified as having an estimated ten-year CVD risk ≥10% (by the Framingham equation) would identify 90% of patients at ≥10% ten-year CVD risk.

No qualitative studies were identified exploring the views of patients or healthcare professionals on cholesterol testing in the context of health checks. Studies on cholesterol screening in the USA 25 years ago identified health consciousness as the main reason for participating in screening.

A number of studies reported patients requesting cholesterol testing in the context of a health check, some GPs considering cholesterol testing the third most important assessment in a health check and other healthcare professionals believing that cholesterol testing could potentially cause unnecessary harm in younger people because of either false reassurance or by creating worry.

There is limited evidence that selective cholesterol testing would have little effect on the identification of patients at high risk of CVD. However, the analyses informing this evidence do not make use of the risk equation currently in use in the UK (QRisk). Indirect evidence suggests patients value cholesterol testing. Some healthcare professionals consider cholesterol testing important and others are concerned about potential harms of testing.

Recommendations

We recommend that analysis is undertaken to assess the effects of selective cholesterol testing on identification of patients eligible for medications to prevent CVD. This should explore a range of selective cholesterol testing strategies, make use of electronic medical records from primary care and use the QRisk equation to determine eligibility for treatment. We also recommend research to elicit patient and professional views on selective cholesterol testing to assess the likely impact on uptake of health checks.

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2. Introduction

The University of Birmingham was commissioned by Public Health England (PHE) to assess the impact of restricting cholesterol testing in NHS Health Check to those with an estimated moderate or high risk score for cardiovascular disease (CVD). This study forms part of a wider review of NHS Health Check for people aged between 40 and 75 years who do not have a pre-existing CVD condition. It builds on a recent rapid evidence review commissioned by PHE into the factors that affect uptake of the NHS Health Check, experiences of patients and management of patients identified as being at risk of CVD. [1]

Health Checks

Figure 1 sets out how the current NHS Health Check programme is delivered. There are local variations in how the programme is delivered. The risk assessment may be provided centrally in some local authorities and in others contracted to individual GP practices. Some patients may receive point of care testing for cholesterol while others may provide blood sample for laboratory testing. The existing programme currently specifies cholesterol testing as part of the risk assessment but its restriction to those identified as moderate to high risk based on other risk factors is being piloted in London (Figure 2).

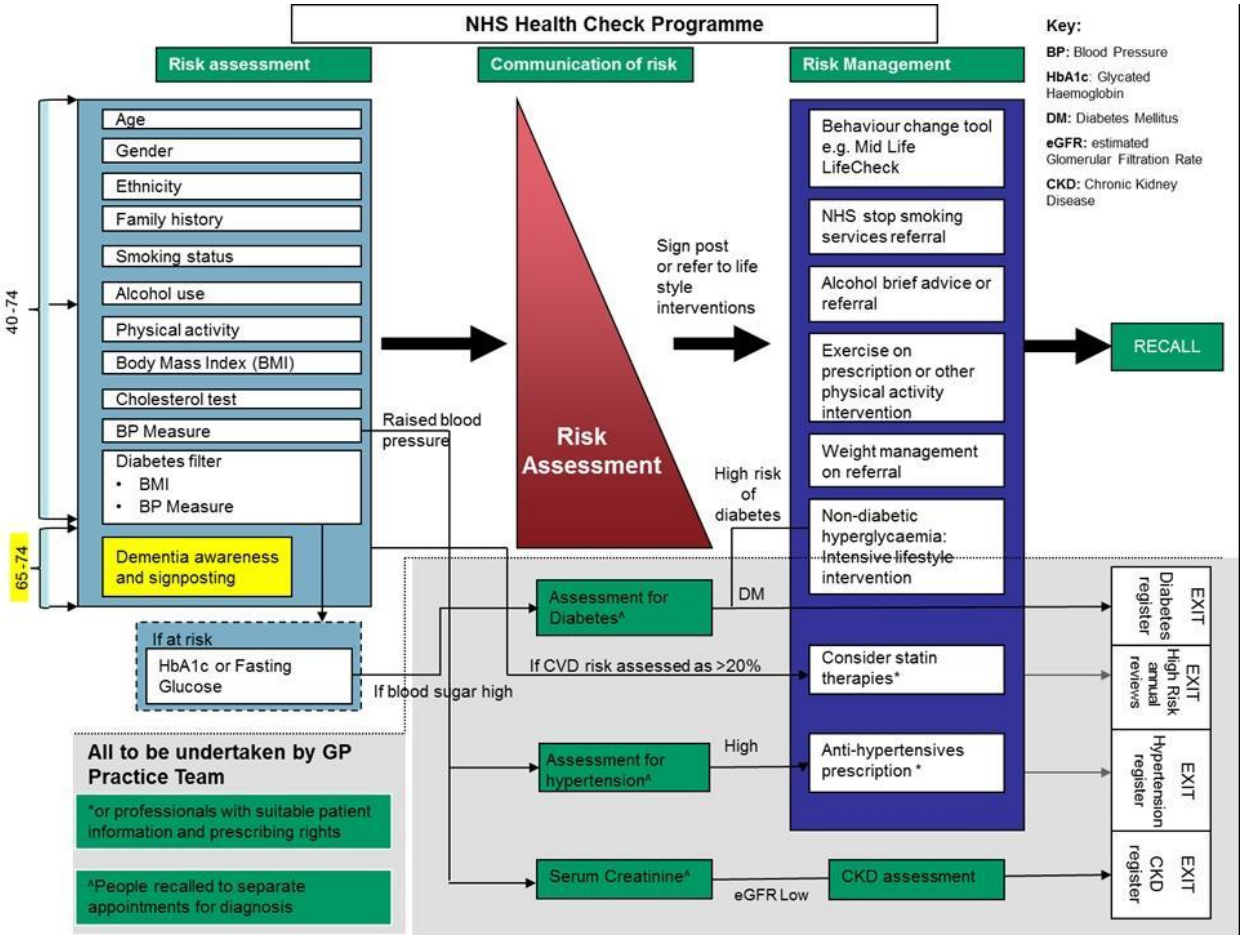

Figure 1. Schematic of how Health Checks are currently delivered

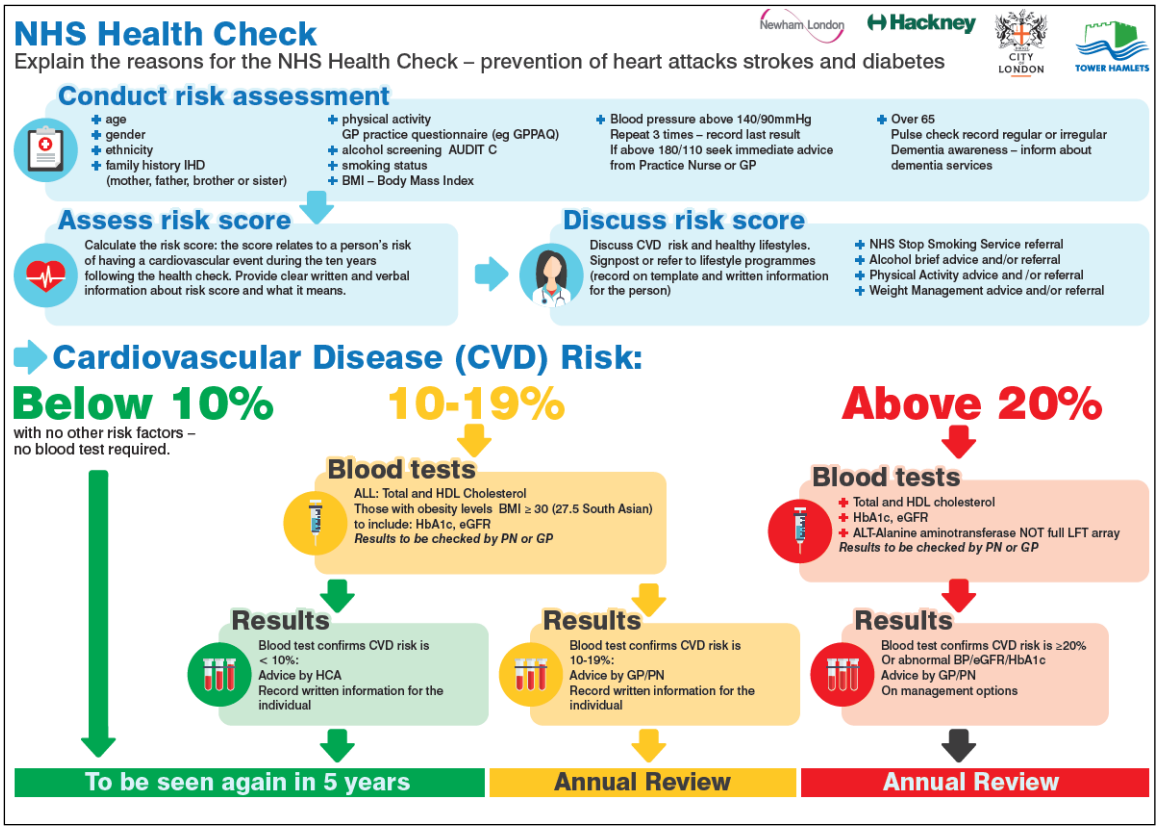

Figure 2. Health Checks in which cholesterol testing is limited to patients with moderate and high CVD risk

Figure 3 and Figure 4 respectively show the potential outcomes of where cholesterol testing is made available to all NHS Health Check attendees and where is restricted to those suspected of being of moderate to high CVD risk. Figure 4 differs from Figure 3 in that it sets out how cholesterol testing might influence different stages in the process and therefore, outcomes for patients. The opportunity to have a cholesterol test may be an incentive to attend an NHS Health Checks for some individuals and therefore, its removal may lead to lower take up by eligible individuals. The decision to use individual's cholesterol test results may influence their risk classification and therefore, the treatment they are offered. Finally, individual's acceptance of and/or adherence to the decision on whether they need treatment and what that treatment should be, may be affected by whether the individual considers cholesterol assessment to be an important component of their health check or a tangible piece of information on which to base lifestyle changes.

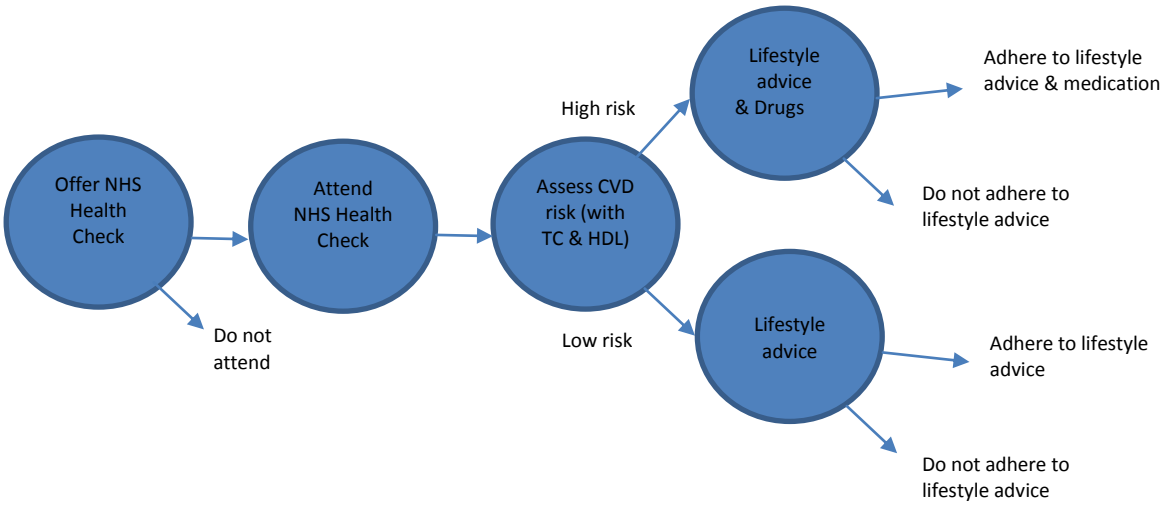

Figure 3. Potential outcomes where cholesterol testing is made available for all attendees

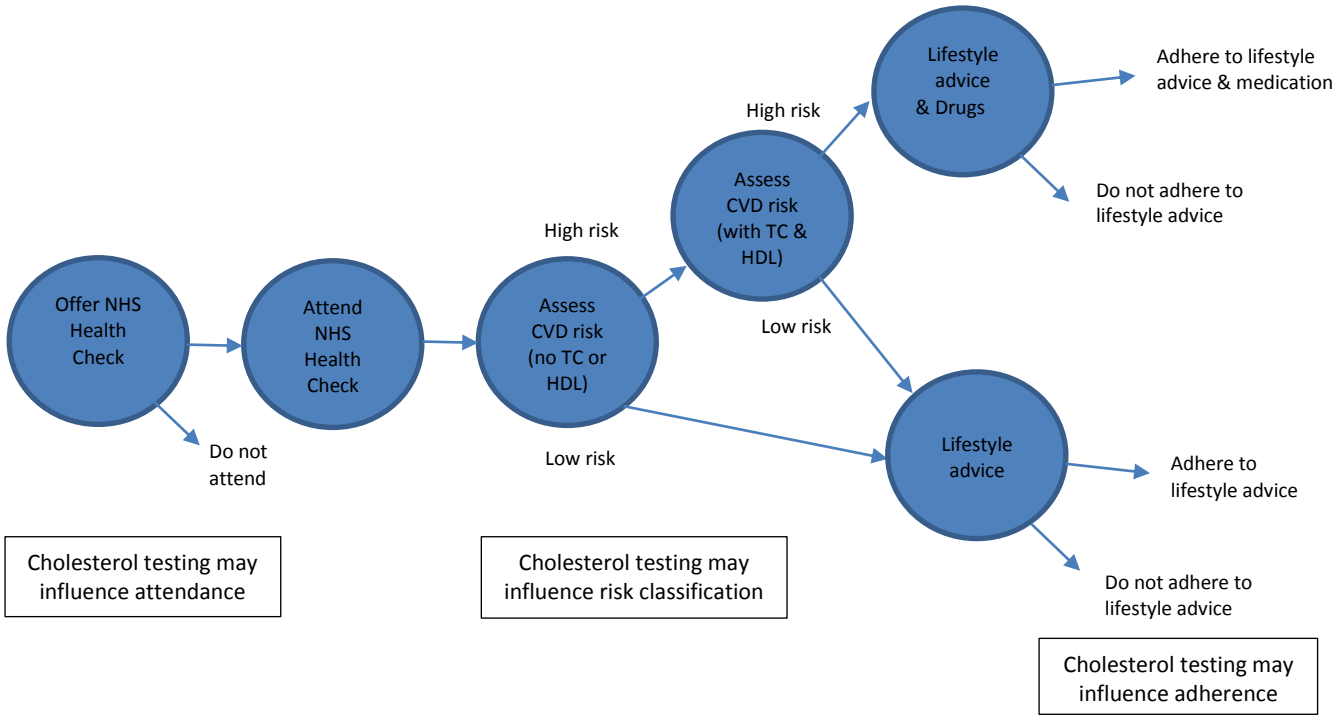

Figure 4. Potential outcomes where cholesterol testing is limited to patients with moderate or high CVD risk

Our initial scoping of the literature identified an evaluation of the first four years of NHS Health Checks,[2] a PhD thesis,[3] local evaluations, research and audits which may provide insights from variations in the service being offered (some of these are published on the PHE website). A review demonstrates how available cardiovascular risk calculators differ in relative risk calculations with identical risk factor increases.[4]

Study Aims

This study aimed to answer the following questions:

Box 1. Research Questions

1	Is there evidence on the impact of restricting cholesterol testing within the NHS Check service, to those who are identified as being at a certain percentage risk of being diagnosed with CVD (10 year risk)?
2	Is there evidence on the impact of restricting cholesterol testing within the NHS Check service, to those who are identified as being at a certain percentage risk of being diagnosed with CVD (lifetime risk)?
3	If so, what is the impact of restricting cholesterol testing within the NHS Health Check service, to those who are identified as being at moderate or high risk of CVD in 10 year; and lifetime risk?
4	If cholesterol testing is restricted, what is the optimal restriction to still ensure the health check is clinically effective for 10 year risk? What is the percentage risk that would be most effective? 10%? 20%? Or restriction to which specific population groups?
5	If cholesterol testing is restricted, what is the optimal restriction to still ensure the health check is clinically effective for lifetime risk? What is the percentage risk that would be most effective? Or restriction to which specific population groups?
6	Is there evidence to suggest that restricting cholesterol testing will change take up of the cardiovascular disease prevention programmes, specifically NHS health check?
7	Is cholesterol testing a deciding factor in why people take up NHS health check?
8	Are there particular groups within the population that this decision would this disproportionally affect in terms of their likelihood to take up the initiative?
9	What would the impact of reducing cholesterol testing have on Familial Hypercholesterolaemia diagnosis?
10	What would the impact of reducing cholesterol testing have on lifetime CVD prevention?
11	How accurate is the QRisk 3 proxy cholesterol calculation for those who have not had a cholesterol test? For both 10 year risk and lifetime risk?
12	Is it possible to use modifiable risk factors for high cholesterol (tobacco use, alcohol, inactivity, weight, diet) as a proxy indicator to whether someone is likely to have high cholesterol? Could these behaviours be used as an additional risk factor as when to test for cholesterol? For both 10 year risk and lifetime risk?

These questions concern the effect of information on total and high density lipoprotein (HDL) cholesterol on classification of individuals as eligible or ineligible for intervention under the NHS Health Checks programme and the effect of cholesterol measurements on predicted lifetime CVD risk using the risk calculators. While the brief specifically asked for information on the 2011 lifetime QRisk equation[5] the effects of including or not including cholesterol test results is likely to be similar in magnitude to the effects on other predictive equations and we therefore, broadened our searches to include other equations that are in common usage. Impact in practice, however, needs to be informed by the lifetime risk thresholds above and below the threshold for testing. The questions are also concerned about the behavioural effects of cholesterol testing: firstly, on uptake (or intended uptake) of Health Checks, and secondly on behavioural change after a Health Check.

3. Methodology

Modification to the original study design

The call by Public Health England asked for the study to be undertaken in two parts. The first part was a rapid evidence review answering the following three questions: (1) Would restricting cholesterol testing to people identified at moderate or high risk of CVD in 10 years, rather than testing everyone as a mandated part of the health check, reduce the clinical effectiveness of the programme? (2) What would the impact of this restriction be on accurately calculating lifetime risk? and (3) Would restricting cholesterol testing among people identified at moderate or high risk of CVD within 10 years, rather than testing everyone as a mandated part of the check, reduce uptake of the programme? The second part was to conduct a systematic review to answer the twelve questions set out in the call. Given the short time scale and volume of studies to be screened it was agreed that both stages would be merged and that questions would be grouped to produce a more coherent synthesis.

Search Strategy

Scoping searches for existing systematic reviews were initially conducted and used to estimate the volume and nature of primary studies and refine our search strategy. Our strategy combined Index terms (e.g. MeSH) with free text words to achieve a sensitive search still capable of precision. Three sets of terms are combined - a set of terms concerning cardiovascular disease, another tests/health checks (including cholesterol testing) and finally a set expressing the concept of risk.

In addition to our main search (Appendix A) we also undertook two additional bespoke searches to identify qualitative studies to answer the questions relating to whether limiting the use of cholesterol testing to individuals identified at moderate or high risk would affect take up and perceived value of health checks. These searches are shown in Appendix B.

Bibliographic databases including MEDLINE (Ovid), EMBASE (Ovid), Cochrane Library CENTRAL and CDSR databases (Wiley) and the Science Citation Index (Web of Science), including CPCI (Conference Proceedings Citation Index) were searched from inception to April 2018. Databases of unpublished (grey) literature were also searched and reference lists of key reviews and other studies located during the search process were examined. No language or publication date restrictions were applied to our searches. The references were managed using EndNote X8 reference management software (Thomson Reuters, New York).

Study selection

Two systematic reviewers (DB, GB) independently first screened titles and abstracts against selection criteria set out in the PICOS statement below (Table 1). Decision on studies to be included was made by consensus and in the absence of consensus, TM acted as an adjudicator. Potential studies that were not excluded were grouped into “Include” where they directly answered one or more of the questions set out above in Box 1 or into “Keep for further consideration” where they might partially answer a question or provide context about the nature of the evidence base. They were then grouped by question. The selection process is illustrated using a PRISMA flow diagram (Figures 5-7).

Table 1. Selection criteria for inclusion and exclusion

Population	Adults aged 40 to 74 without diagnosis of CVD and not being treated for, or on the register for diabetes, chronic kidney disease or hypertension. Stratified by risk; low (<10%), medium (<20%) and high (>20%)
Intervention	Health Check
Comparator	With and without cholesterol testing
Outcome	10 year risk of CVD Lifetime risk Uptake and acceptance by patients Any other outcome relevant to this review
Study Design	The research questions outlined in the call require drawing on evidence from a range of quantitative and qualitative study designs

Data extraction and synthesis

Since no studies were directly related to the review questions, a simple data extraction form was developed including basic information on study design and findings of interest. Data of some potentially interesting studies was extracted by one reviewer, and a second reviewer checked and provided quality assurance. Synthesis of evidence was undertaken separately for the different evidence review questions. Narrative synthesis of evidence was conducted for all relevant studies with the extracted data to be tabulated. Due to lack of evidence that could answer the review questions meta-analyses and quality assessment were not conducted.

4. Findings

The main literature search identified 2,502 records. Of those 2,394 title and abstracts were screened against pre-determined eligibility criteria and 99 full texts were selected as potentially relevant. Since no studies were identified that could directly answer any of the 12 review questions, 27 studies were selected as of potential interest. The selection process is illustrated in Figure 5.

A more targeted approach was adopted in order to identify qualitative studies relating to NHS Health Checks (Figure 6). Out of the 588 records initially identified 28 were considered for full text eligibility. No studies met all of the pre-determined eligibility criteria. Thus, 9 studies were selected that explored experiences and views of patients and healthcare professionals as part of an evaluation of Health Check programmes.

In addition, a bespoke search was performed combining terms relating to cholesterol tests and screening or qualitative research evidence in order to capture studies that focus mainly on cholesterol testing. The searches identified 652 records. Of those 18 full texts were assessed for eligibility. Once again no studies were identified that could directly answer any of the review questions; however, 6 studies were considered further that provided context about the nature of the evidence base specifically for questions 6, 7 (programme uptake) and 9 (familial cholesterolaemia). The selection process is illustrated in Figure 7.

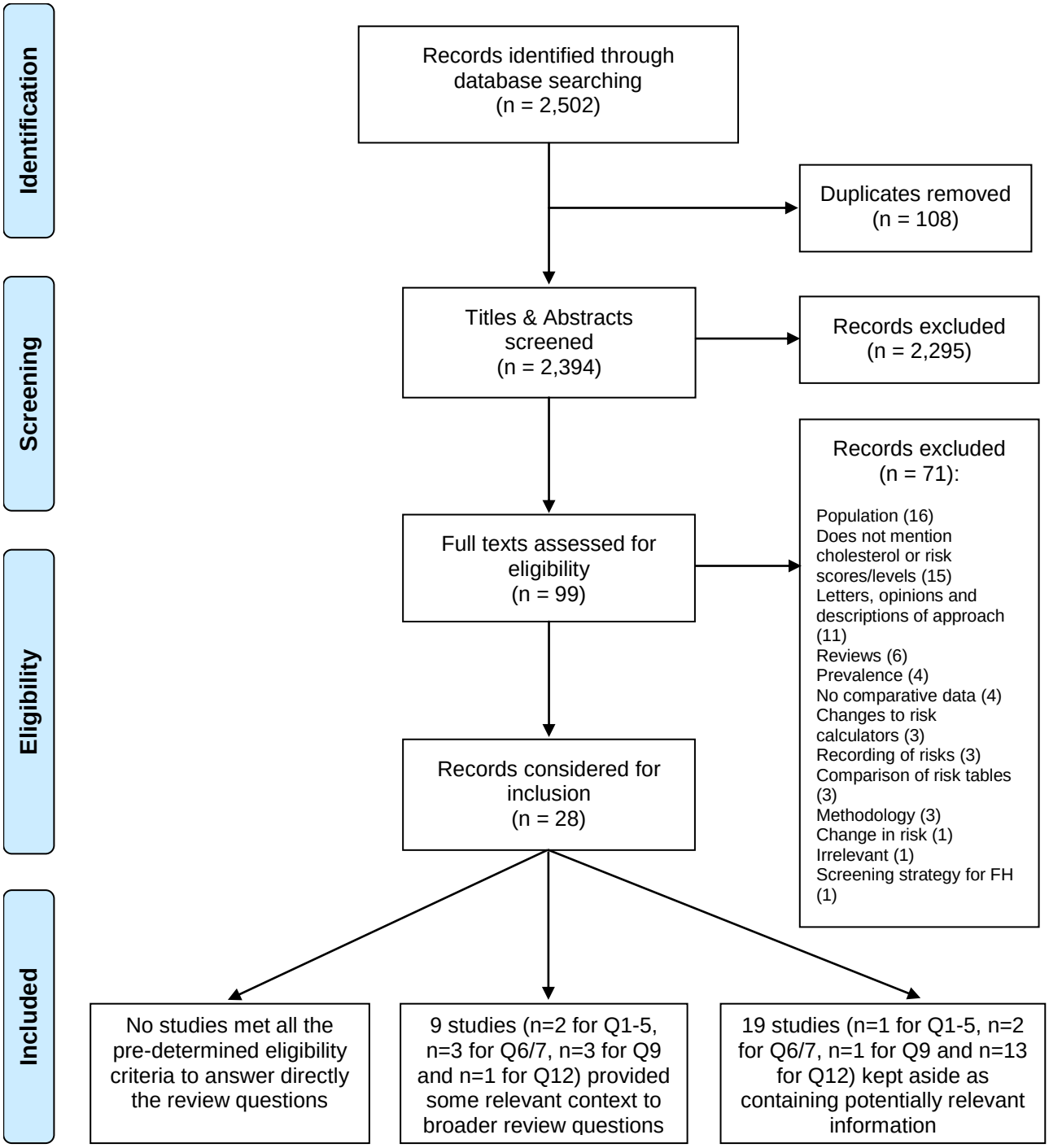

Figure 5. PRISMA flow diagram for study selection of main searches

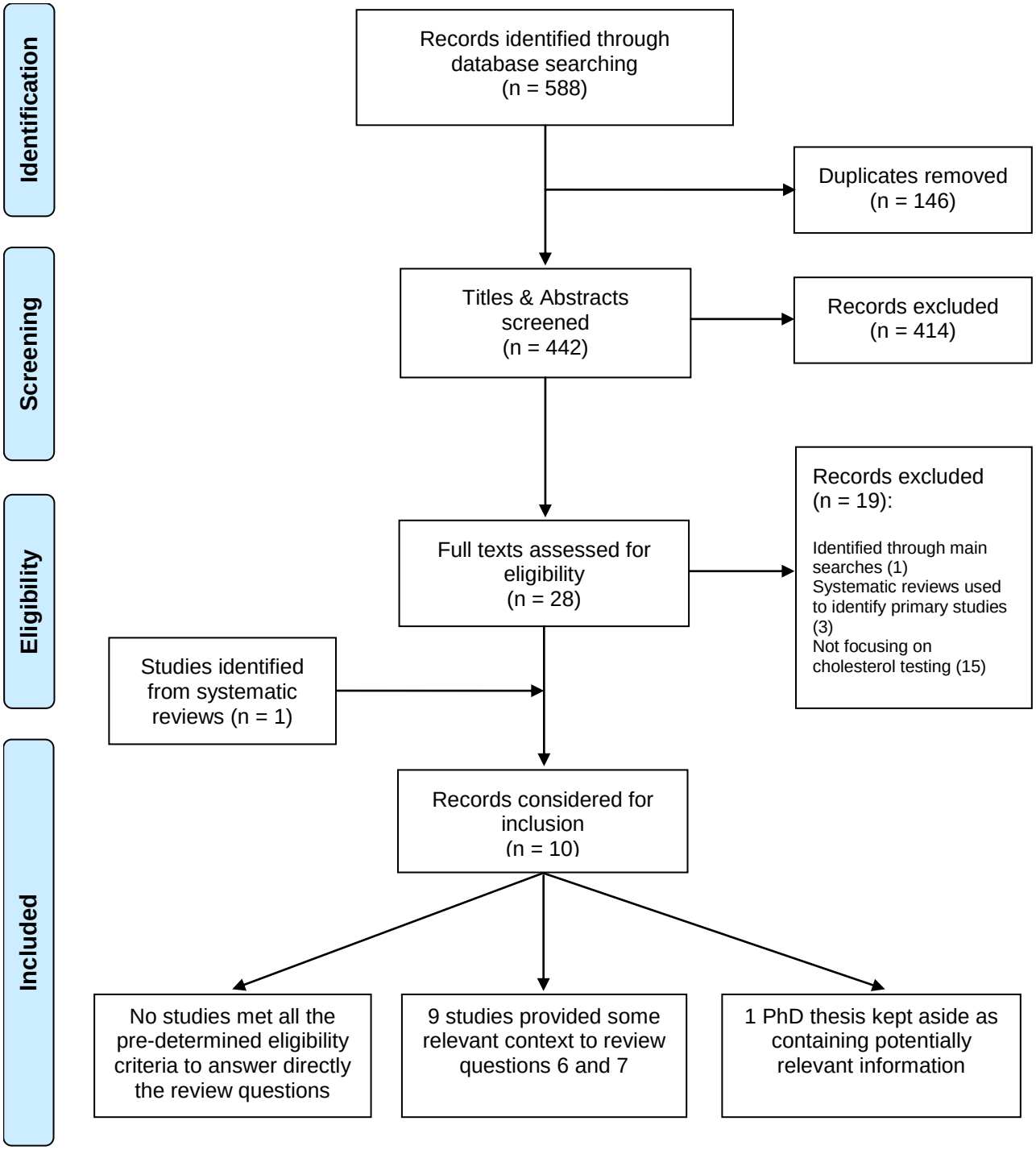

Figure 6. PRISMA flow diagram for study selection of Health Check searches targeted to identify qualitative studies

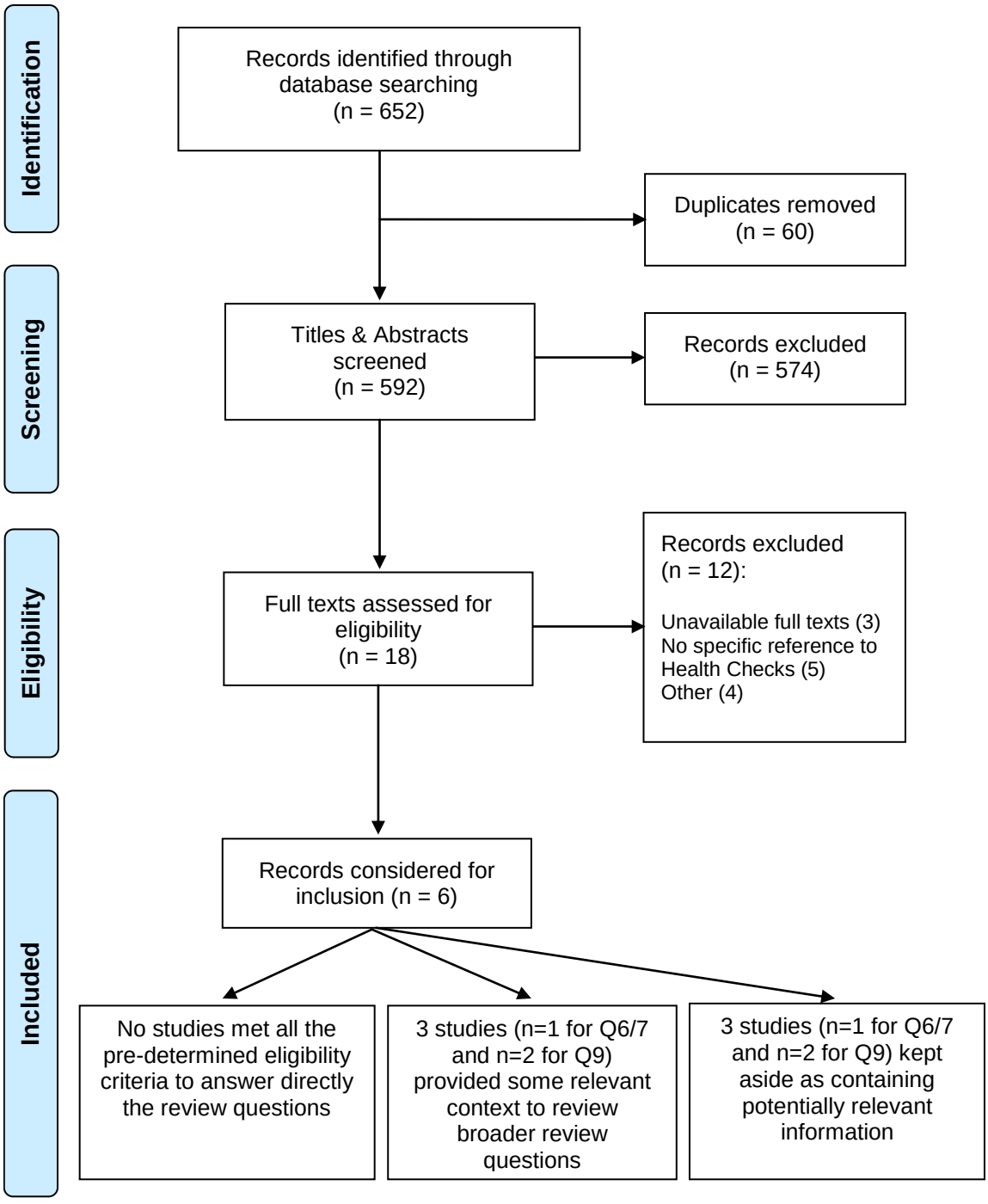

Figure 7. PRISMA flow diagram for study selection of targeted cholesterol testing searches to identify qualitative studies

Impact of restricting cholesterol testing to patients identified with moderate to high risk of CVD

The brief included the following questions relating to the impact of restricting cholesterol testing to patients identified as moderate to high risk:

- Is there evidence on the impact of restricting cholesterol testing within the NHS Check service, to those who are identified as being at a certain percentage risk of being diagnosed with CVD (10 year risk)?
- Is there evidence on the impact of restricting cholesterol testing within the NHS Check service, to those who are identified as being at a certain percentage risk of being diagnosed with CVD (lifetime risk)?
- If so, what is the impact of restricting cholesterol testing within the NHS Health Check service, to those who are identified as being at moderate or high risk of CVD in 10 year; and lifetime risk?
- If cholesterol testing is restricted, what is the optimal restriction to still ensure the health check is clinically effective for 10 year risk? What is the percentage risk that would be most effective? 10%? 20%? Or restriction to which specific population groups?
- If cholesterol testing is restricted, what is the optimal restriction to still ensure the health check is clinically effective for lifetime risk? What is the percentage risk that would be most effective? Or restriction to which specific population groups?

Our searches found no studies specifically answering these questions. While we identified studies that described the implementation of NHS Health Checks and evaluations of its implementation in different areas, none of these studies provided any comparative data restricting the use of cholesterol testing to individuals identified as being of moderate to high risk of CVD event in next years.

There were, however, three studies that only partially answered these questions (Table 2).

The Second Northwick Park Heart Study[6] was a prospective cohort study of 3,052 males with a mean follow-up of 10.8 years. The study reports 219 events in 2,732 men (with complete data) including 153 acute coronary heart disease (CHD) events, 45 coronary artery revascularisation procedures and 21 silent myocardial infarctions (MIs). The study reports average cholesterol value of 5.69 (SD 1.00) for 1,258 males who had no CHD and 6.05 (SD 1.02) those that developed CHD. The hazard ratio for cholesterol (uncorrected for age) was calculated to be 1.26 (1.04-1.52, p=0.02), which was broadly similar to systolic blood pressure (HR 1.23 (1.02-1.48, p=0.03), triglyceride levels (HR 1.23 (1.02 – 1.48, p=0.03) and Fibrinogen (HR 1.29 (1.07-1.55, p=0.001). Smoking (HR 1.61 (1.10-2.35, p=0.02), diabetes (HR 3.10 (1.14-6.80, p=0.005) and family history (HR 1.67 (1.15-2.44, p=0.007).

The same study also provides information on AUC and false-positive rate where average value for HDL and LDL cholesterol is used in calculating risk using Framingham and PROCAM equations, which could be considered a proxy for not testing for cholesterol. For both PROCAM and Framingham equations the AUC values were almost identical [0.58 (0.50-0.66) when average value is used and 0.59 (0.52-0.67) when actual values are used for PROCAM; 0.61 (0.55-0.67) and 0.62 (0.55-0.68) for Framingham equation]. The use of average values resulted in half as many false-positives for PROCAM (12.8% compared to 8.6% when using individual values). The difference was as great with Framingham (8.4% compared to 7.5%).[6]

Karmali et al. (2014)[7] study calculates 10-years absolute risk for atherosclerotic cardiovascular disease (non-fatal MI, non-fatal stroke and fatal CVD) using Pooled Cohort Equations that are available as a spreadsheet. The authors model the effect of cholesterol at different levels on predicted risk in four hypothetical cases non-Hispanic white male, non-Hispanic white female, African-American male and African-American female. Age was varied in each case in five year increments between 40 and 75 years and single risk factors were varied in isolation holding other factors constant at age adjusted mean values. The study provides information on total cholesterol. The modelling suggests, while there is a linear relationship with total cholesterol and curvilinear relationship with HDL cholesterol, age banding was more significant in exceeding the intervention level set 7.5% predicted 10-year ASCVD risk.

The third unpublished study (Marshall 2018) assesses the effects of different cholesterol testing strategies on identification of patients eligible for drug treatments to prevent cardiovascular disease. The study population was selected from the Health Survey for England 1998. It includes all individuals aged 40 to 74 years on whom complete cardiovascular risk factor information is available. Because patients on disease registers are excluded from Health Checks, patients who already had a diagnosis of CVD or diabetes or who were already receiving antihypertensive therapy were excluded. Patients with an irregular pulse were also excluded as this was assumed to indicate atrial fibrillation. Ten-year CVD risk was calculated using the Framingham risk equation from the available risk factor information: age, sex, smoking status, diabetic status, systolic blood pressure, total cholesterol and HDL cholesterol levels.[8] This was taken to be the true CVD risk (CVD_{True}). Rules for determining treatment eligibility were based on NICE guidelines.[9 10] The strategy of offering cholesterol testing to 53% of the population (with 10-year $CVD_{Estimated}$ ≥10%) identified 90% of individuals eligible for treatment and there were no false-positives. This unpublished study still however does not fully answer the question of the impact of limiting cholesterol testing in NHS Health Checks to individuals identified as having moderate to high CVD risk: further research is needed using more recent datasets such as THIN, and by utilising the more commonly used QRisk equation.

Table 2. Overview of included studies relating to impact of restricting cholesterol testing to patients identified with moderate to high risk of CVD

<table>
<tr><th>Author, Date, Country</th><th>Study design</th><th>Findings</th><th>Main Conclusions, comment</th></tr>
<tr>
<td>Cooper (2005), England[6]</td>
<td>Second Northwick Park Heart Study (NPHS-II)

Prospective cohort (Median follow-up 10.8years). 3052 Caucasian males recruited from 9 general practices who completed a questionnaire on lifestyle and medical history.

Compared predictive value of PROCAM and Framingham risk algorithms in healthy UK men (50-64years at entry).

Endpoint: coronary heart disease event (acute CHD events, sudden coronary death, fatal myocardial infarction). Details of CHD events were obtained general practices, hospitals and coroners offices.

Clinical history, ECGs, cardiac enzymes and pathology were assessed by independent panel according to World Health Organisation criteria.

Data collected from HPHS-II were used to develop a risk score. 2732 men were randomly assigned to 2 groups (one to develop the score, the other to test it). This initially included the same variables as the Framingham equation, replacing HDLC with plasma triglyceride level.</td>
<td>219 CHD events in 2732 men (with complete data at January 2004) including 153 acute CHD events, 45 coronary artery revascularisation procedures and 21 silent MIs.

Serum HDLc and LDLc were not measured at baseline and values were set to the average observed in a subset of 2000 men over 5 year follow up period (LDLc 4.0 mmol/L and HDLc 0.8mmol/L).

ROC area (PROCAM, 0.63 [95% CI, 0.59-067); Framingham, 0.62 [95% CI, 0.58-0.66], p=0.46]. There was a modest increase in ROC, 0.64 (95% CI, 0.58-0.70)

Table 2.1. Associations between CHD and risk factors
<table>
<tr><th>Factor</th><th>No CHD mean (SD) N=1258</th><th>CHD mean (SD) N=110</th><th>Hazard ratio (95% CI)</th><th>p-value</th></tr>
<tr><td>Age (years)</td><td>56.0 (3.5)</td><td>56.4 (3.7)</td><td>1.19 (0.90-1.56)</td><td>0.22</td></tr>
<tr><td>Systolic blood pressure (mmHg)</td><td>137.7 (19.1)</td><td>143.1 (18.9)</td><td>1.23 (1.02-1.48)</td><td>0.03</td></tr>
<tr><td>Cholesterol (mmol/L)</td><td>5.69 (1.00)</td><td>6.05 (1.02)</td><td>1.26 (1.04-1.52)</td><td>0.02</td></tr>
<tr><td>Triglyceride (mmol/L)</td><td>1.77 (0.93)</td><td>2.14 (1.18)</td><td>1.23 (1.02-1.48)</td><td>0.03</td></tr>
<tr><td>Smoking (%)</td><td>27.8%</td><td>38.6%</td><td>1.61 (1.10-2.35)</td><td>0.02</td></tr>
<tr><td>Diabetes (%)</td><td>1.7%</td><td>6.1%</td><td>3.10 (1.41-6.80)</td><td>0.005</td></tr>
<tr><td>Family history (%)</td><td>34.3%</td><td>46.4%</td><td>1.67 (1.15-2.44)</td><td>0.007</td></tr>
<tr><td>Fibrinogen (g/L)</td><td>2.69 (0.51)</td><td>2.58 (0.53)</td><td>1.29 (1.07-1.55)</td><td>0.001</td></tr>
<tr><td>Lp(a) (% >26.3mg/dL)</td><td>22.4%</td><td>32.4%</td><td>1.60 (1.05-2.42)</td><td>0.03</td></tr>
</table>
Table 2.2. Comparison of using average and individual HDL and LDL values
<table>
<tr><th></th><th></th><th>AUC (95% CI)</th><th>False positive rate ±</th></tr>
<tr><td>PROCAM</td><td>Average value</td><td>0.58 (0.50-0.66)</td><td>12.8%</td></tr>
<tr><td></td><td>Individual value</td><td>0.59 (0.52-0.67)</td><td>8.6%</td></tr>
<tr><td>Framingham</td><td>Average value</td><td>0.61 (0.55-0.67)</td><td>8.4%</td></tr>
<tr><td></td><td>Individual value</td><td>0.62 (0.55-0.68)</td><td>7.5%</td></tr>
</table>
± Sensitivity rate for a 5% false-positive rate</td>
<td>The authors conclude that despite the inclusion of variables that are strongly and independently associated with CHD, all three systems (PROCAM, Framingham and a risk score created from NPHS-II data) showed modest discrimination, and sensitivities are well below those need for a screening tool. The inclusion of new risk factors may, as they identified, improve scoring.</td>
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<table>
<tr>
<td>Karmali (2014), USA [7]</td>
<td>10-year absolute risk for atherosclerotic cardiovascular disease (ASCVD) (includes nonfatal MI, nonfatal stroke, and fatal CVD) was calculated using Pooled Cohort Equations. This is a spreadsheet that can be downloaded. It includes sex and race specific models that incorporate age, total and HDLc, systolic blood pressure, use of antihypertensive medicine, smoking status and diabetes. Models pooled data from several contemporary studies.

The authors developed hypothetical cases that they entered into the spreadsheet:

• Non-Hispanic white man
• Non-Hispanic white woman
• African-American man
• African-American woman

Aged was varied for each case between 40-75years in 5 year increments.

Single risk factors were varied in isolation, holding other factors constant at age-adjusted mean values to compare the effects of individual risk factors on 10-year predicted risk for each hypothetical case.

Multiple risk factors were also varied around the national mean level to examine the effects of different risk factor combinations on 10-year estimated ASCVD risk. Ranges were inclusive of low and modestly abnormal values. Total cholesterol included values of 1.6mmol/L (≈1 SD below the mean), 2.0mmol/L (approximate national mean) and 2.4mmol/L (≈1 SD above the mean).</td>
<td>Authors present results in graphs. 10-year risk increases linearly by age for total cholesterol, untreated and treated systolic blood pressure in all 4 cases. However, this was much less pronounced for cholesterol than SBP. Whereas, there was curvilinear relationship for HDL Cholesterol.

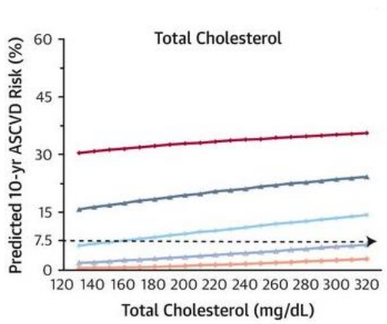
Figure 2.1. Non-Hispanic white man
 

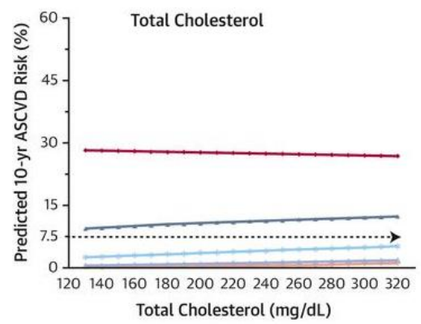
Figure 2.2. Non-Hispanic white woman
 

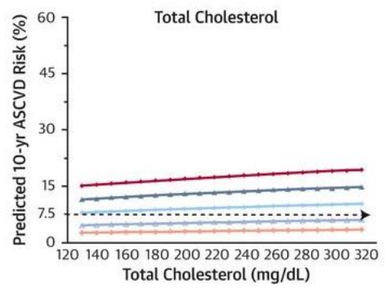
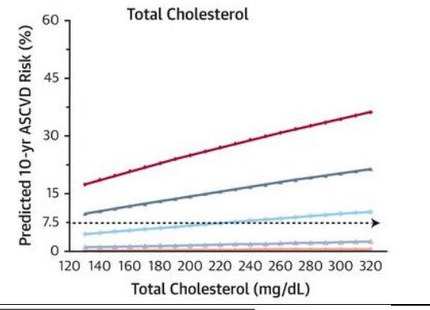
Figure 2.3. African-American man
 

Figure 2.4. African-American woman
 

 
</td>
<td>The authors conclude:

The updated ACC/AHA cholesterol guidelines recommend the use of newly derived Pooled Cohort Equations to estimate 10-year ASCVD risk. The present study provides context of specific risk factors levels and groups of individuals who are likely to have 10-year ASCVD risk estimates exceeding 7.5%.

Compared with the ATP III risk assessment tool, the inclusion of stroke endpoints and the use of race-specific coefficients permits identification of at-risk women and African-Americans at much younger ages and at lower risk factor levels. Age continues to be a major driver of 10-year ASCVD risk, which highlights the importance of the clinician-patient discussion before initiation of initiation of statin therapy.</td>
</tr>
<tr>
<td>Marshall (Unpublished)</td>
<td>This analysis extends some work undertaken for the PhD thesis completed in 2004. It investigates the effects of including or excluding routine assessment of cholesterol levels on identification of patients at high risk of cardiovascular disease (CVD).

The study population was selected from the Health Survey for England 1998. It includes all individuals aged 40-74 on whom complete cardiovascular risk factor information is available. Because patients on disease registers are excluded from Health Checks, patients who already had a diagnosis of CVD or diabetes or who were already receiving antihypertensive therapy were excluded. Patients with an irregular pulse were also excluded as this was assumed to indicate atrial fibrillation.</td>
<td>The study population included 3950 individuals of whom 2137 (54%) were eligible for either antihypertensive or statin treatment (or both), based on their true CVD risk (Table 2.3) Younger female individuals were infrequently eligible for treatment whereas almost all older male individuals were eligible for treatment. Of those eligible for at least one treatment, the great majority (97%) were eligible for statins.

Table 2.3. Study population and proportion eligible for any treatment (either antihypertensives or statins)
<table>
<tr><th></th><th colspan="3">Total population</th><th colspan="3">Numbers eligible for any treatment</th><th colspan="3">Proportion eligible for any treatment</th></tr>
<tr><th>Age band</th><th>Men</th><th>Women</th><th>Both</th><th>Men</th><th>Women</th><th>Both</th><th>Men</th><th>Women</th><th>Both</th></tr>
<tr><td>40-44</td><td>380</td><td>405</td><td>785</td><td>104</td><td>27</td><td>131</td><td>27%</td><td>7%</td><td>17%</td></tr>
<tr><td>45-54</td><td>699</td><td>863</td><td>1562</td><td>450</td><td>203</td><td>653</td><td>64%</td><td>24%</td><td>42%</td></tr>
<tr><td>55-64</td><td>413</td><td>544</td><td>957</td><td>396</td><td>337</td><td>733</td><td>96%</td><td>62%</td><td>77%</td></tr>
<tr><td>65-74</td><td>319</td><td>327</td><td>646</td><td>319</td><td>301</td><td>620</td><td>100%</td><td>92%</td><td>96%</td></tr>
<tr><td>All ages</td><td>1811</td><td>2139</td><td>3950</td><td>1269</td><td>868</td><td>2137</td><td>70%</td><td>41%</td><td>54%</td></tr>
</table></td>
<td>A strategy of offering cholesterol testing to 53% of the population (with ten-year $CVD_{Estimated}$ ≥10%) identifies 90% of individuals eligible for treatment.

Shortcomings of this analysis

<u>Prevalence of eligibility for treatment</u>
This analysis uses the Framingham CVD equation rather than the QRisk2 calculator to estimate 10-year CVD risk. Framingham risks tend to be significantly higher than those estimated from QRisk2

Contribution of cholesterol levels to risk prediction

The importance of cholesterol as a predictor of CVD also differs between the Framingham and QRisk2 equations. In practice, the Framingham equation includes six predictors: age, sex, diabetic status (yes/no), smoking status (yes/no),</td>
</tr>
</table>

10-year CVD risk and eligibility for treatment

10-year CVD risk was calculated using the Framingham risk equation from the available risk factor information: age, sex, smoking status, diabetic status, systolic blood pressure, total cholesterol and HDL cholesterol levels. This was taken to be the **true** CVD risk (CVD_{True}).

Rules for determining treatment eligibility were based on NICE guidelines.

Eligibility for treatment

Treatment	Eligibility criteria
Statins	10-year CVD risk ≥10%
Statins	Familial hypercholesterolaemia (i.e. total cholesterol ≥9 mmol/L)
Antihypertensives	Blood pressure ≥160/100 mm Hg (either systolic or diastolic)
Antihypertensives	Blood pressure ≥140/90 mm Hg (either systolic or diastolic) AND ten-year CVD risk ≥10%

Identification strategies

The total number of individuals eligible for statins or antihypertensives was determined using the true 10-year CVD risk (CVD_{True}) and recorded risk factors. This was determined for each age and sex group.

The proposed strategy is to **estimate CVD risk without the cholesterol levels and to undertake cholesterol measurements only in individuals whose estimated 10-year CVD risk (without cholesterol levels) is greater than 10%.**

A true CVD risk would therefore be available only for those individuals whose estimated 10-year CVD risk was greater than 10%. To reflect this:

- The 10-year CVD risk was recalculated without total cholesterol and HDL cholesterol levels. This uses a method previously described in the doctoral thesis.
- For each individual the average cholesterol and HDL levels for a person of that age and sex is used instead of their measured cholesterol and HDL cholesterol levels. This is the estimated CVD risk ($CVD_{Estimated}$).
- The average cholesterol and HDL levels were derived from the Health Survey for England 1998.

Twenty seven individuals had total cholesterol levels greater than 9 mmol/L (81% female, 70% aged 55 to 74) and were therefore considered to have familial hypercholesterolaemia.

Under a strategy of using the 10-year $CVD_{Estimated}$ and only using CVD_{True} if $CVD_{Estimated}$ was ≥10%, 1919 individuals were identified as eligible for any treatment. All of those identified as eligible for treatment were also eligible for treatment on the basis of their CVD_{True} in other words, under this strategy there were no false positive results. This is a sensitivity of 90% (95% CI: 88% to 91%) and a specificity of 100% (95% CI: 99% to 100%).

Table 2.4. True positive and test positive results with a selective cholesterol testing strategy for identification of patients eligible for any treatment

		True eligibility for treatment		
		Yes	No	Total
Eligibility based on identification strategy	Yes	1919	0	1919
	No	218	1813	2031
	Total	2137	1813	3950

False negative men (missed patients eligible for at least one treatment) were almost all (98%) men aged under 55 years or and 98% of false negative women were aged under 65 years.

Sensitivity by age, sex and treatment eligibility

The sensitivity of a selective cholesterol testing strategy is highest in the older age groups (Table 2.5) and is higher for detecting eligibility for antihypertensive treatment than for detecting individuals at greater than 10% 10-year CVD risk (Table 2.6).

Table 2.5. Sensitivity of a selective cholesterol testing strategy for identification of patients eligible for any treatment or for antihypertensives: by age and sex

Age band	Sensitivity: eligibility for any treatment			Sensitivity: eligibility for antihypertensives		
	Men	Women	Both	Men	Women	Both
40-44	62%	67%	63%	97%	93%	96%
45-54	86%	71%	82%	99%	97%	98%
55-64	99%	87%	94%	100%	100%	100%
65-74	100%	99%	100%	100%	100%	100%
All ages	92%	87%	90%	100%	99%	99%

Table 2.6. Sensitivity of a selective cholesterol testing strategy for identification of patients at ≥10% 10-year CVD risk or with Familial Hypercholesterolaemia: by age and sex

Age band	Sensitivity: ≥10% 10-year CVD risk			Sensitivity: FH (TC ≥9.0 mmol/L)		
	Men	Women	Both	Men	Women	Both
40-44	54%	41%	52%	0%	0%	0%
45-54	86%	63%	79%	100%	0%	17%
55-64	99%	87%	94%	100%	78%	80%
65-74	100%	99%	100%	100%	100%	100%
All ages	91%	85%	89%	80%	64%	67%

The selective testing strategy does not detect familial hypercholesterolaemia in younger age groups, because few of these individuals undergo cholesterol testing.

Number of individuals who undergo cholesterol testing

Under the strategy of universal cholesterol testing all 3950 individuals in the study population undergo cholesterol testing.

Under the strategy of selective cholesterol testing 2082 individuals (53% of the study population) were identified as having a 10-

systolic blood pressure and the ratio of total to HDL cholesterol. As diabetic patients are excluded from health checks, total to HDL cholesterol ratio is one of five predictors in the population eligible for health checks.

QRisk2-2015 includes 14 predictors: age, sex, deprivation banding, ethnicity (eight categories), diabetic status (type 1 or type 2), smoking status (four categories), family history of premature coronary heart disease, chronic kidney disease, rheumatoid arthritis, atrial fibrillation, antihypertensive treatment, Body Mass Index, systolic blood pressure and total to HDL cholesterol. As diabetic patients, those taking antihypertensives and those with atrial fibrillation are excluded from health checks, total to HDL cholesterol ratio is one of ten predictors in the population eligible for health checks.

QRisk3 includes 22 predictors (23 if systolic blood pressure variability is considered a separate variable to systolic blood pressure) of which total to HDL cholesterol ratio is one.

Definition of Familial Hypercholesterolaemia

The true frequency of familial hypercholesterolaemia is not known. The assumption that a total cholesterol of ≥9 mmol/L is equivalent to a diagnosis of familial hypercholesterolaemia gives a prevalence of 0.7% in the study population. However not all patients with familial hypercholesterolaemia have a total cholesterol of ≥9 mmol/L and not all those with a total cholesterol of ≥9 mmol/L have familial hypercholesterolaemia.

Implications of the shortcomings

It is not possible to know the sensitivity of the selective cholesterol testing strategy if QRisk2 (or QRisk3) were used instead of Framingham. Sensitivity could be higher because cholesterol levels are only one of many predictors in the QRisk equations. But it could be lower because the exact contribution of cholesterol to the QRisk equations is not known.

Using QRisk to determine eligibility for treatment, fewer individuals will be eligible for treatment than in this analysis. It is unclear what effect this will have on sensitivity. However, under a selective cholesterol testing strategy fewer individuals will be identified as having $CVD_{Estimated}$ ≥10% and therefore fewer will undergo cholesterol testing.

	• If their 10-year $CVD_{Estimated}$ was less than 10% these individuals were considered not to be eligible for statin treatment. • If their 10-year $CVD_{Estimated}$ was greater than 10% their treatment eligibility was determined from their CVD_{True} and recorded risk factors. • The number of individuals identified as eligible for statins or antihypertensives was determined using this combination of $CVD_{Estimated}$ and CVD_{True}.	year $CVD_{Estimated}$ ≥10% and therefore undergo cholesterol testing.	

Table 3. Overview of included studies identified through the main search relating to the effects of restricting cholesterol testing on take up of health checks

<table>
<tr><th>Author, Date, Country</th><th>Study design</th><th>Findings</th><th>Main Conclusions</th></tr>
<tr><td>Harris, Backlund 1989a[11]

USA</td><td>Part of suite of three papers reporting on population screening for plasma cholesterol in three communities.

Each participant completed a questionnaire and signed a consent form before blood sample was taken.

Blood was collected by finger puncture with a sterile lancet (Bostin Dickerson & Co, Franklin Lakes, NJ) and collected into 300µL vials by capillary action, which contain lithium heparin as an anticoagulant.

Blood analysed at screening sites to allow for immediate return of results to participants using Kodak Ektachem DT-60 Analyzers (Eastman Kodak, Rochester, NY).

Using values set by NHLBI Consensus Conference levels were reported back as desirable, moderate or high risk.

Nutritional information was made available to all participants and those in moderate or high risk category were referred to their physician for retesting and evaluation. If the participant with high risk did not have a physician they were provided names of physicians willing to accept new patients in participating hospitals.</td><td>Total screened 10,672 (5,689 females; 4,983 males) of which 2,875 were male aged 41-70 and 3,435 were female aged 41-70.

Table 3.1. Reason for participation and mean cholesterol levels by white men and women
<table><tr><td></td><td colspan="2">White Men</td><td colspan="2">White Women</td></tr><tr><td></td><td>N = 4,484</td><td>Mean cholesterol (mg/dl) [95% CI)</td><td>N = 5,013</td><td>Mean cholesterol (mg/dl) [95% CI)</td></tr><tr><td>Health conscious</td><td>2,480 (55.3%)</td><td>192 [2]</td><td>2,552 (50.9%)</td><td>197 [2]</td></tr><tr><td>Curiosity</td><td>732 (16.3)</td><td>191 [3]</td><td>619 (12.4%)</td><td>199 [3]</td></tr><tr><td>Family History</td><td>488 (10.9%)</td><td>198 [4]</td><td>633 (12.6%)</td><td>201 [3]</td></tr><tr><td>Prior high cholesterol</td><td>423 (9.4%)</td><td>222 [4]</td><td>550 (10.9%)</td><td>225 [4]</td></tr></table>
Table 3.2. Reason for participation and mean cholesterol levels by black men and women
<table><tr><td></td><td colspan="2">Black Men</td><td colspan="2">Black Women</td></tr><tr><td></td><td>N = 298</td><td>Mean cholesterol (mg/dl) [95% CI)</td><td>N = 417</td><td>Mean cholesterol (mg/dl) [95% CI)</td></tr><tr><td>Health conscious</td><td>162 (54.3%)</td><td>182 [13]</td><td>232 (55.6%)</td><td>198 [7]</td></tr><tr><td>Curiosity</td><td>83 (11.9%)</td><td>180 [14]</td><td>79 (18.9%)</td><td>193 [10]</td></tr><tr><td>Family History</td><td>9 (6.3%)</td><td>205 [30]</td><td>32 (7.7%)</td><td>206 [15]</td></tr><tr><td>Prior high cholesterol</td><td>20 (6.7%)</td><td>206 [22]</td><td>27 (6.5%)</td><td>222 [16]</td></tr></table>
Individuals were categorised slightly different to Harris et al. 1989b in that the >20 was divided into 21-30 and >30 cigarette per day. The same trend for increasing cholesterol levels by cigarette smoked was reported but no</td><td>Mass screening is a necessary component of a national cholesterol education effort because so many individuals are unsuspected of high serum cholesterol levels and could be helped. There should be targeting of groups that participate less in mass screening, particularly young individuals, smokers and minority groups.

Public Health officials should strive for public knowing their cholesterol value as early in life as possible.</td></tr>
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<table>
<tr>
<td></td>
<td></td>
<td>figures provided. Ex-smokers had similar cholesterol levels to those who do not smoke.</td>
<td></td>
</tr>
<tr>
<td>Harris, Harley 1989b[12]

USA</td>
<td>Part of suite of three papers reporting on population screening for plasma cholesterol in three communities.</td>
<td>Total screened 7,338 (4,103 females; 3,235 males) of which 1,969 males aged 41 -70; 2,691 females aged 41-70.

Those screened were older and more educated than the average United States population and did not reflect the population of Miami (82% white c.f. 67%; 6.5% black c.f. 27%).

Table 3.3. Reason for participation and mean cholesterol levels by men and women
<table>
<tr><td></td><td colspan="2">Men</td><td colspan="2">Women</td></tr>
<tr><td></td><td>N = 3,235</td><td>Mean cholesterol (mg/dl) [95% CI)</td><td>N = 4,103</td><td>Mean cholesterol (mg/dl) [95% CI)</td></tr>
<tr><td>Health conscious</td><td>1,654 (50.8%)</td><td>209 [±2]</td><td>1,806 (44.0%)</td><td>221 [±2]</td></tr>
<tr><td>Curiosity</td><td>389 (11.9%)</td><td>212 [±4]</td><td>385 (9.4%)</td><td>223 [±4]</td></tr>
<tr><td>Family History</td><td>206 (6.3%)</td><td>216 [±6]</td><td>303 (7.4%)</td><td>229 [±5]</td></tr>
<tr><td>Prior high cholesterol</td><td>476 (14.6%)</td><td>241 [±4]</td><td>799 (19.5%)</td><td>256 [±3]</td></tr>
</table>
Individuals were categorised into 0, 1-10, 11-20, >20 cigarettes per day and ex-smokers. There was a general increase in the level of cholesterol with increasing number of cigarettes smoked per day for all categories [0.5 mg/dl per cigarette] except women over age 50.</td>
<td>The data suggests that at least for the health conscious segment of the population that avails itself of cholesterol screening, the identification of risk factors, physician involvement and the reduction of cholesterol can be a public health success.</td>
</tr>
<tr>
<td>Wynder 1989[13]

USA</td>
<td>Study tool place in Hartford, Connecticut using the same methodology as Harris</td>
<td>Total screened 15,892 (9,019 females; 6,433 males) of which 3,871 males aged 41-70; 5,694 females aged 41-70. Less than 1.5% were black. Lower percentage cigarette smokers than general population [12% c.f. 30%].

Table 3.4. Reason for participation and mean cholesterol levels by men and women
<table>
<tr><td></td><td colspan="2">Men</td><td colspan="2">Women</td></tr>
<tr><td></td><td>N = 6,433</td><td>Mean cholesterol (mg/dl) [95% CI)</td><td>N = 9,019</td><td>Mean cholesterol (mg/dl) [95% CI)</td></tr>
<tr><td>Health conscious</td><td>3,538 (54.9%)</td><td>200 [2]</td><td>4,613 (51.4%)</td><td>203 [2]</td></tr>
<tr><td>Curiosity</td><td>1,074 (16.7%)</td><td>201 [3]</td><td>1,180 (13.1%)</td><td>204 [3]</td></tr>
<tr><td>Family History</td><td>442 (6.8%)</td><td>207 [4]</td><td>864 (9.5%)</td><td>210 [3]</td></tr>
<tr><td>Prior high cholesterol</td><td>569 (8.8%)</td><td>229 [4]</td><td>832 (9.2%)</td><td>233 [3]</td></tr>
</table>
Individuals were categorised slightly different to Harris et al. 1989b in that the >20 was divided into 21-30 and >30 cigarette per day. The same trend for increasing cholesterol levels by cigarette smoked was reported but no figures provided. Ex-smokers had a similar cholesterol levels to those who do not smoke.</td>
<td>Same as Harris (a)</td>
</tr>
</table>

The effects of restricting cholesterol testing on take up of health checks

The brief included three specific questions regarding patient (and health care professionals) attitudes to cholesterol and cholesterol testing that these might affect take up of health checks amongst the targeted population.

- Is there evidence to suggest that restricting cholesterol testing will change take up of the cardiovascular disease prevention programmes, specifically NHS health check?
- Is cholesterol testing a deciding factor in why people take up NHS health check?
- Are there particular groups within the population that this decision would this disproportionally affect in terms of their likelihood to take up the initiative?

Following a comprehensive literature search no qualitative studies have been identified specifically exploring the views of patients attending and healthcare professionals involved in the NHS Health Checks in relation to the usefulness of cholesterol testing and/or its impact on programme uptake if selective screening is implemented.

Our main searches identified studies on screening for high cholesterol. There were a number of public health campaigns to educate general public about cholesterol in the late 1980s and 1990s that predate NHS Health Checks and their international equivalent. There was one set of studies that reported on the same interventions in three different locations in the USA that report on reasons why participants took part in cholesterol screening (Table 3).[11-13] In all three locations participants were not representative of the wider population being typically older or more educated, ethnic minorities were underrepresented and there were some gender differences. Together, the three studies included 33,902 participants. Across all three studies, health consciousness was the most prevalent reason for participating in cholesterol screening and this was higher in men than women (ranging from 50.8% to 54.9% c.f. 44.0% to 51.4% across the studies). Other factors such as curiosity (13.75%), family history (9.02%) and previously high cholesterol levels (11.19%) were much less common reasons for participation across all the studies (our own calculations). However, it should be noted these studies were undertaken in the USA over 25 years ago and therefore, the findings may lack direct relevance.

Ten qualitative studies are presented in this report as containing some interesting information regarding health checks and cholesterol testing (Table 4). Five studies[14-18] were conducted in UK with the NHS Health Check programme either piloted or well implemented in the general practices, 2 studies[19 20] were conducted in The Netherlands where a cardiometabolic health check is available, 2 studies[21 22] explored experiences in the Danish health service for cardiovascular risk assessment and 1 study[23] was conducted in Ireland where an asymptomatic general check-up (AGCU) is in place. Five[14 16-18 21] out of the 10 studies presented here draw conclusions regarding patients and healthcare professionals' experiences of and attitudes towards health checks with some participants' quotes referring to cholesterol levels but within a more general context of understanding the usefulness of health checks and identifying barriers to attendance. However, the remaining 5 studies presented more specific views on cholesterol testing. Ismail et al. (2015)[15] and Van Steenkiste et al. (2004)[20] reported a request (or even a demand in cases of elderly patients) from people attending health

checks for having a cholesterol test. This view is reinforced by some GPs (19%) considering cholesterol testing as the third most important item that should be performed in the AGCU consultation.[23] In contrast, some healthcare professionals believe that cholesterol testing could potentially cause unnecessary harm (negative feelings) in younger people or those with "elevated risk" due to providing false security in cases of favourable results or additional fear/worry if risk is misinterpreted.[19 22]

Table 4. Overview of included studies identified through bespoke searches relating to the effects of restricting cholesterol testing on take up of health checks

Author, year, country	**Study Design**	**Findings**	**Main Conclusions**
Ismail 2016, UK[14]	Aim: exploring issues related to uptake, understanding of the programme and experiences of behavioural changes from the patients' perspective. Semi-structured interviews (30-45min) with 45 patients (24 men and 21 women with an average age of 58) attending a Health Check. 35 followed up 1 year later to assess whether the behavioural changes suggested had been maintained. 5 practices in Leeds (3 in the most deprived quintile; 2 in more mixed areas economically). Framework approach for data analysis by Silverman D. 2006.	Main themes and references to cholesterol testing: 1. <u>Understanding</u> There was confusion about the Health Checks from some patients who associated it with a visit to the surgery for a variety of reasons (e.g. *cholesterol* or blood pressure check or weight measurement) and not specifically CVD. When probed on the reasons for attending the Health Check, patients' primary objectives were to ensure they were in good health . . . to identify whether they were suffering from a condition such as diabetes, high blood pressure or *high cholesterol*. 2. <u>Advice from health professionals</u> There was some confusion over the results of *cholesterol scores*. Only 6 interviewees could recall their score although most patients had a sense of whether their score was good or bad. A written confirmation would have been helpful. An opportunity to discuss health matters in depth in a follow-up appointment. *"I think I have a very good relationship with my doctor . . . So yes, we talked, she explained the difference between good and bad cholesterol" (49-year-old White female).* 3. <u>Barriers encountered in changing behaviour</u> (i) smoking cessation (ii) physical activity (iii) healthy eating (iv) alcohol consumption	No specific conclusions relating to cholesterol testing.

Ismail 2015, UK[15]	Aim: explore the challenges and barriers faced by staff involved in the delivery of the NHS Health Check. 3 sites across the Yorkshire region of the UK including 25 general practices. In depth interviews (25-45min) with 30 HCAs, 5 GPs, 9 practice managers, 14 practice nurses (n=58). Framework approach for data analysis by Silverman D. 2006.	Main themes and references to cholesterol testing: 1. Invitation to attend 2. Awareness-raising 3. Barriers to behaviour change 4. Organisational barriers 5. Training requirements 6. Effective team working 7. Perceptions of the benefits and drawbacks of Health Checks Positive views: • Help to identify and support people with *high cholesterol*, high blood pressure or diabetes, as well as heavy smokers and heavy drinkers. • *Many people wanted a cholesterol check*.	Request from people attending Health Checks to have a cholesterol test.
Murphy 2015,[23] Ireland	Aim: to research Irish GP experiences with the AGCU. Mixed-method study surveying 79 GPs (63% male; mean age 50 years) in the Northwest of Ireland. Open-text boxes were used for qualitative analysis.	Of 11 blood tests, eight were deemed (extremely) important by a majority of GPs, in the following order (greatest importance first): glucose/HbA1c screening (73%), *cholesterol/lipids*, full blood count, urea/electrolytes, liver function tests (51%), PSA test if male (45%), thyroid function tests and lastly ferritin iron studies (34%). Overall, cholesterol testing was third most important item which GPs felt should be performed in the AGCU consultation (19% of respondents).	GPs place cholesterol testing third in the list of the 20 items that should be performed in health checks.
Jenkinson 2015, UK[16]	Aim: identify factors influencing patients' willingness to attend an NHS Cardiovascular Health Check (NHSHCs). Telephone or face-to-face	Main themes and references to cholesterol testing: 1. <u>Factors influencing uptake</u> (i) Motivators to attend (ii) Barriers to attendance Some non-attendees felt the NHSHC was unnecessary due to their receiving regular monitoring for other health conditions, or having their blood pressure	No specific conclusions relating to cholesterol testing.

	interviews with 27 patients (17 attendees and 10 non-attendees) who had recently been invited for an NHSHC from 4 general practices in Torbay, England. Patients were stratified by gender and age (either 40-65 years or 66-74 years) in an attempt to recruit people of different working status. Thematic analysis used.	or *cholesterol* recently checked. 2. <u>NHSHC experience</u> Many interviewees reported receiving simple lifestyle advice *"Er, I just watch the amount of um, butter and fat levels I have that might affect my cholesterol, yeah, just become a little bit aware of that, which I wasn't before. That's about it." (Attendee, male, retired, 66 years)* 3. <u>Engagement in future NHSHC</u> 4. <u>Recommendations for improvements to the NHSHC</u>	
Riley 2015, UK[18]	Aim: investigate the experiences and views of patients attending and HCPs conducting NHS Health Checks. Semi-structured interviews (20-60min) with 28 patients, 5 GPs, 5 practice nurses, 3 HCAs, 2 pharmacists conducted between April 2013 and February 2014. Patient records from 8 primary care practices in Bristol from a range of socio-economic backgrounds. Health Check done within the previous 6 months. 7 patients aged 40-59 and 21 aged over 60. 11 patients of high risk, 11 of medium risk and 6 of low risk.	Main themes and references to cholesterol testing: 1. <u>Motivations for attending a health check</u> 2. <u>Communicating results and lifestyle advice</u> Feeling uncertain about the significance of their results and lack of information/lifestyle advice to support them in making changes: *"my cholesterol is high . . . What does that mean? I've got no idea what that means. It sounds bad because it's higher than it's meant to be but is it? And it was that kind of information which was the kind of the bit beyond, you know, eat less, exercise more, don't smoke, don't drink . . . that would have been useful that didn't really seem to be part of what was on offer there . . ." (Female 60–64 years, low risk)* *"I understand it [cholesterol result] is now on the high side of the normal. Whatever that means . . . because it was only a receptionist that told me and . . . So it would have been helpful to have spoken to maybe a nurse or . . . you know, a word from the GP would have been helpful." (Female 65–69 years, medium risk)* 3. <u>Implications of attending an NHS Health Check</u>	No specific conclusions relating to cholesterol testing.

	15 HCPs from the same 8 practices plus 3 more. 4 were 25-44 years and 11 45-64 years mainly females. Thematic analysis used.	(i) reassurance, reinforcement and relief *"going through various sort of checks . . . like cholesterol . . . and talking about my diet, it . . . reinforced and made me think . . . I'm actually doing all the things I probably should be doing." (Female 50–54 years, low risk)* (ii) anxiety provoking *"sometimes some people are in shock really, especially when it comes to the cholesterol, they think, Oh my God, I didn't know it was that high." (HCA)* (iii) behaviour change *"I did make a concerted effort and . . . did lose a bit more weight . . . because coupled with like high cholesterol and blood pressure, I thought oh a dodgy combination." (Female 65–69 years, medium risk)*	
Perry 2014, UK [17]	A small-scale qualitative study exploring experiences of engaging with a community-based NHS Health Check in Knowsley, England (area with high prevalence of CVD) 3 focus groups and 6 semi-structured interviews with 36 individuals (17 males and 19 females) who had received a health check, 12 with a high-risk CV score and 24 with a low-risk CV score. A variety of community settings and venues used (such as local supermarkets, shopping centres, the library) for the health checks.	Main themes and references to cholesterol testing: 1. <u>Engagement with a health check</u> Underlying health problems were also part of the explanation for having a health check. *"Well I've had a bit of a problem, you know with cholesterol and I thought "Oh I'll get it checked just to see how it was." (HR.INT2)* 2. <u>Understanding of the risk score</u> 3. <u>Changing behaviour as a consequence of the health check</u> The health check had acted specifically as a wake-up call *"I think what happens, it's like a reality check when, you know, two and half stone over weight, your cholesterol is high and you know your life expectancy, them three things, it's a bit of a shock even though you know . . . , when it actually gets written down and presented to you, it becomes reality." (HR.INT5)*	No specific conclusions relating to cholesterol testing.

Godefrooij 2014, Netherlands[19]	Aim: to explore the implementation of a cardiometabolic health check as perceived by the involved caregivers and patients. 3 focus groups of care professionals (5 medical receptionists, 3 practice nurses and 5 GPs) and an open-ended questionnaire for collecting 657 (52% of 1270) patients' experiences. 5 general practices of the Woensel Healthcare Centre in Eindhoven, Netherlands participated in the CMD prevention programme. Thematic content analysis used based on grounded theory principles.	Main themes and references to cholesterol testing: 1. <u>Offering and receiving primary prevention</u> (i)Screening versus case-finding (ii) Importance of primary prevention, offered by GPs (iii) Contents of the health check (iv) Yield of the health check The practice nurses thought that the yield of the health check was high: many thus far unknown cases had been identified. *"What I really noticed was how many people with latent disease, or elevated blood glucose levels we have identified. And how many people with a well elevated LDL cholesterol"* 2. <u>Division of tasks</u> (i) Delegation of care (ii) Preparation and knowledge 3. <u>Approaching the participants</u> (i) Dealing with healthy patients (ii) Communicating the results, avoiding unnecessary harm In most of the cases the elevated "risk" was rather innocent: e.g. a slightly elevated blood glucose or *cholesterol level*. The GPs and practice nurses felt that these patients were unnecessarily harmed by this approach. (iii) Providing room for questions Patients that did not have an elevated risk were not invited for a follow-up consultation. However, they would have liked more detailed information about their results and the opportunity to ask questions. *"I didn't get anything to take home. Nothing that I can use to compare in future examinations: cholesterol levels, blood pressure, other blood results, weight"*	HCPs recognised the fact that more people with elevated cholesterol levels were detected; however, this elevated risk was not always interpreted correctly by participants and this in turn could cause unnecessary harm.

		4. <u>Follow-up after the health check</u> (i) Importance of follow up and continuing care (ii) Integration of the health check with everyday clinical practice	
Søndergaard 2012, Denmark[22]	Aim: GPs' attitudes towards and concerns about providing preventive health checks. The Danish Health Service does not provide this service, but health checks are nevertheless being conducted unsystematically. 3 semi-structured focus group interviews with 16 GPs (mean age 53 years) from Jutland, Denmark (Central Region).	Main themes and references to cholesterol testing: 1. <u>Diversity in the delivery of health checks</u> 2. <u>The GPs' ambivalence towards health checks</u> Several informants considered prevention to be an important part of their work, while others viewed health checks as peripheral to their field of work. *"We are fed up maintaining cholesterol levels. We want to do something else. Retired schoolteachers could do that job. It is more an educational thing than a doctor's."* The risk of inducing negative psychological reactions and false security by performing health checks worried several of the GPs. *"Concerning these young people, I think that it (the health checks) does them more harm than good. My personal view is, talk about health, but don't measure their cholesterol level."* 3. <u>The GPs' request for clarification</u>	Cholesterol testing in younger people might cause more harm (negative psychological reactions and false security) than good according to some GPs.
Neilsen 2009, Denmark[21]	Aim: to explore how individuals whose health screening does not reveal a high CV risk score interpret and respond to this result. Qualitative semi-structured interviews with 7 men and 15 women aged 36-50 years with a low or moderate CV risk score participating in a Danish health-screening project.	Main themes and references to cholesterol testing: 1. <u>The expert confirmed the participants' feeling that they were all right</u> Some participants mentioned their *cholesterol count*, since cholesterol was much discussed in the media at that point. A 37-year-old football referee said it was good to know: *". . . in your everyday life that you're not about to have a coronary . . . after all your cholesterol count could easily be too high . . . ."* 2. <u>No more worries</u> The participants said it was good to have got the all-clear, and to get rid of worries concerning fitness, weight, *cholesterol level*, or family health problems.	No specific conclusions relating to cholesterol testing.

	Analysis and interpretation were informed by the Health Belief Model and by Hollnagel and Malterud's theories.	3. <u>There is a price to be paid for the reassurance</u>	
van Steenkiste 2004, Netherlands[20]	Aim: to explore those barriers that impede effective communication on CV risk and prevention during consultations in primary care. 15 GPs in the southern part of the Netherlands recruited the first two consecutive patients (aged 40-70 years) without established CVD that he or she met in a consultation to discuss a patients' CV risk. Each patient (n=22; mean age 52±8.6) was interviewed 1–2 weeks after the consultation. Thematic content analysis used following grounded theory rules.	Main themes and references to cholesterol testing: 1. <u>Barriers related to patients' ideas about CVD and risk factors</u> (i) Understanding CV diseases (ii) Understanding CV risk factors Patients often overestimated the importance of *cholesterol* as a risk factor or even perceived *cholesterol* as the most important risk factor. *"Cholesterol is more dangerous than high blood pressure, as a clot may become detached and go to your brain."* *"If your cholesterol is elevated, it means some blood vessel is blocked."* 2. <u>Barriers related to patients' risk perception (fears)</u> CV risk did not seem to be a clear concept to many patients. Dichotomous thinking: "*If your cholesterol is good, it means you no longer run a risk of CVD."* 3. <u>Expectations for information and treatment</u> (i) Expectations concerning health information and education They might be well-informed about their low risk, but nevertheless are anxious about monitoring their *cholesterol level*. *"I know I should believe what the doctor says, but then afterwards I start to think what if it's not OK, and then I get another blood sample tested. I think you should get a health check once a year."* (ii) Expectations about interventions/management of problems The patient's reason for encounter was often a request (or even demand) for a *cholesterol test.* Right to a cholesterol test (among the elderly): *"If I want to know, I feel it's my right to know."*	There was a need for more information on cholesterol as a CV risk factor. There was a request or even demand (especially amongst the elderly) for a cholesterol tests and appropriate treatment.

		Despite the GP's explanation about the relative weight of one abnormal risk factor in the entire risk profile, some patients were not convinced and still asked for medication. Uniform approach: *"My brother also has a cholesterol level of 6 and he gets the pills."* *"I had 6.3 mmol/L serum cholesterol and my GP would not give me those pills. I know, there are all kinds of other factors involved, but my uncle also had high cholesterol and no risk factors and he still had a heart attack. Give me those tablets anyway."* Some patients explained that regular check-ups of blood pressure and serum cholesterol reduced their fear of becoming dependent. *". . . I never used to think about that before, but now I do. Life's too good to want to die now. Maybe, I should have a cholesterol check-up every 6 months now that I'm almost 60. It does not mean I'm old, but the risk of getting something is increasing."*	

Familial Hypercholesterolaemia

The prevalence of heterozygous FH in UK is estimated to be 1 in 500, suggesting that 120,000 people are affected. The elevated serum total (>7.5 mmol/L) and LDL (>4.9 mmol/L) cholesterol concentrations that characterise heterozygous FH lead to a greater than 50% risk of coronary heart disease by the age of 50 in men and at least 30% in women aged 60.[24]

In 2008, NICE published a clinical guideline for the Identification and Management of FH (CG71; updated in 2017).[25] The guideline recommends identifying cases of FH, using cholesterol measurements and cascade screening of first- and second-degree relatives of index cases. The NHS Health Check programme is testing all adults in England aged 40-74 years for cholesterol levels and could be considered as one of the strategies to detect people with FH which is complementing cascade testing.

The PHE brief included a question on the impact of restricting cholesterol testing on identification of index cases and screening for familial hypercholesterolaemia.

- What would the impact of reducing cholesterol testing within the NHS Check service, to those who are identified as being at a certain percentage risk of being diagnosed with CVD, have on Familial Hypercholesterolaemia diagnosis?

Main literature searches alongside bespoke searches have not identified any evidence that could answer the question above. Most of the available evidence on FH focused on the effectiveness of different diagnostic and identification strategies (e.g. opportunistic screening, universal screening of children, cascade screening of family members) in a number of settings (e.g. primary care, specialised lipid clinics) and in populations of a broad age range (Appendix C). Two qualitative studies were kept aside that might give some insight to public awareness relating to hereditary lipid disorders and barriers to diagnosis of FH in women (Appendix D).

Five studies are presented in this report all conducted in UK that might be of some interest (Table 5). A study by Boregowda et al. in 2013[26] stretched the importance of cholesterol screening of healthy individuals aged >40 years in the general population. The authors reported an incidence of FH being 2.5 in 500 in people with no family history of hypercholesrerolaemia or premature cardiac disease. However, this study is presented as a conference abstract with limited information and a follow-up article with final study results could not be found.

Bhatnagar et al. in 2000[27] investigated the effectiveness of cascade screening of first-degree relatives of 259 index cases. The authors suggested that population screening for high cholesterol concentrations should be undertaken as part of a wider approach to detect people with FH linking primary care with lipid clinics something that is also evident in the NICE guidelines.

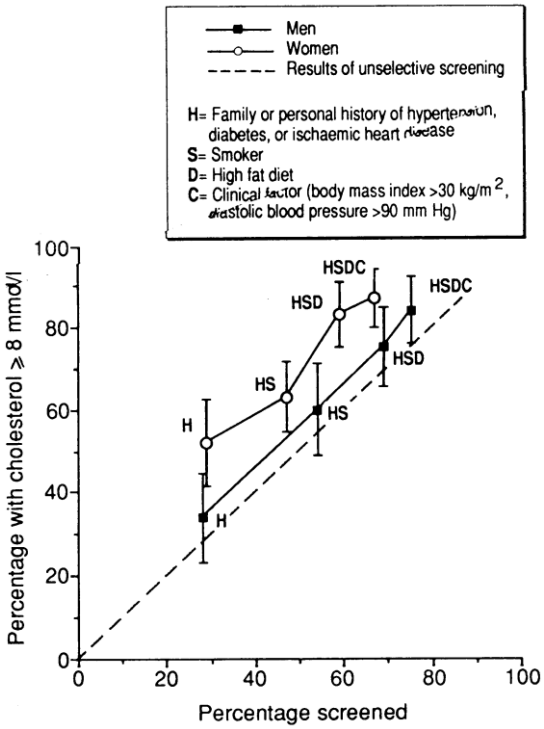
A not so recent RCT by Muir et al. in 1991[28] explored the possibility of selective screening using risk factors (including family history of hypertension, diabetes and ischemic heart disease, smoking, high fat diet, BMI) to determine who should have a cholesterol test. None of the suggested strategies seemed to be much better than unselective screening in identifying patients with hyperlipidaemia. It should be noted that although the population in this study is within the required age-range for an

NHS Health Check, more than a quarter of them in the 55-64 age group already had a diagnosis of heart disease, hypertension or diabetes. Thus, it is not a cohort of healthy individuals.

Finally, 2 studies (Nherera et al. 2011[29] and Marks et al. 2000[30]) estimated the cost effectiveness of different diagnostic strategies for FH. The general notion was that cascade screening from index patients is the most cost-effective strategy to identify new cases of FH than universal screening alone.

Table 5. Overview of relevant studies relating to the diagnosis of Familial Hypercholesterolaemia

Author, year, country	Study Design	Findings	Main Conclusions
Boregowda 2013, UK[26]	In abstract form only. 790 healthy individuals (aged >40 years) attending voluntary Health Check-up. NICE criteria for diagnosis of definite FH. Outcome: Total cholesterol levels	8 healthy individuals with total cholesterol >7.5 mmol/L; of which 4 with no family history of hypercholesrerolaemia or premature IHD. 29 healthy individuals with total cholesterol >6.5 mmol/L but <7.5 mmol/L; of which 22 with no family history of hypercholesrerolaemia.	Reported incidence 5 in 500; of which 2.5 in 500 with no family history of hypercholesrerolaemia or premature cardiac disease.
Bhatnagar 2000, UK[27]	Two lipid clinics in central and south Manchester. 259 index cases (137 men with a mean age 45.0 ± 11.4 years; 122 women with a mean age 48.9 ± 12.6 years) and 200 first degree relatives tested. Simon Broome criteria for diagnosis of FH. Outcome: newly diagnosed patients	Of 200 relatives tested for serum cholesterol concentrations, 121 new cases were identified (60%; 46 men and 75 women; all younger than the index cases).	Because 1 in 500 people in the UK are affected by FH, to detect a similar number of new cases by population screening over 60,000 tests would be required, and only a few of these patients would have been detected had cholesterol testing been restricted to those with other risk factors for coronary heart disease.
Muir 1991, UK[28]	The OXCHECK (Oxford and collaborators health check) RCT. 2205 middle-aged (35-64 years) patients who attended for a Health Check in 1989-90. The cohort was from an invited random sample of	The total cholesterol concentration was ≥6.5 mmol/L in 37% of patients and ≥8 mmol/L in 8%. The figure shows the proportion of the population screened and the proportion of patients with appreciable hypercholesterolaemia (total cholesterol concentration ≥8 mmol/L) detected by four selective strategies.	The proportion of patients in whom cholesterol concentration would be measured if a selective screening policy were adopted would vary from 29% to 71%,

	2777 patients from five general practices in Luton and Dunstable, Bedfordshire. Some patients already diagnosed with IHD, hypertension or diabetes. Outcome: total cholesterol concentration	Measuring cholesterol concentration only in those with a family history of premature IHD (aged <60 years) in a first degree relative or with a personal history of IHD, diabetes, or hypertension would require 29% of the population to be screened and will detect 44% of those with a total cholesterol concentration ≥8 mmol/L, whereas if all available indices of risk are used the figures increase to 71% and 86%. **Figure 5.1.** Percentage of patients with various risk factors eligible for screening and percentage with total cholesterol concentration ≥8.0 mmol/L that would be detected using different criteria for screening  	according to different criteria, but (particularly in men) no combination would be much better than random testing as a means to detect patients with a total cholesterol concentration ≥8 mmol/L.

<table>
<tr>
<td>Nherera 2011, UK[29]</td>
<td>Probabilistic economic evaluation (cost utility analysis) comparing 4 screening strategies:

1. Cholesterol – elevated LDL cholesterol levels in affected relatives
2. DNA – genetic testing of index case and first-degree relatives
3. DNA + DFH – cascade testing of relatives of DFH with or without mutations
4. DNA + DFH + PFH – cascade testing of relatives of DFH and PFH with or without mutations

Hypothetical 1000 patients referred from GPs with suspicion of FH aged 50 years for index cases and 30 years for relatives, followed for a lifetime.

Outcome: costs, QALY, ICER</td>
<td>Table 5.1. Number of index cases and relatives identified by the four cascade strategies
<table>
<tr><th rowspan="2">Outcome</th><th colspan="4">Cascade strategies</th></tr>
<tr><th>Cholesterol</th><th>DNA</th><th>DNA+DFH</th><th>DNA+DFH+PFH</th></tr>
<tr><td colspan="5">Cases (n=1000)</td></tr>
<tr><td>True +ve</td><td>480*</td><td>420*</td><td>450*</td><td>480*</td></tr>
<tr><td>False –ve</td><td>0</td><td>60</td><td>30*</td><td>0</td></tr>
<tr><td>False +ve</td><td>420*</td><td>420</td><td>420</td><td>420*</td></tr>
<tr><td>True -ve</td><td>100</td><td>100</td><td>100</td><td>100</td></tr>
<tr><td colspan="5">Relatives</td></tr>
<tr><td>True +ve</td><td>765</td><td>1338</td><td>1385</td><td>1433</td></tr>
<tr><td>False –ve</td><td>430</td><td>0</td><td>27</td><td>53</td></tr>
<tr><td>False +ve</td><td>497</td><td>0</td><td>33</td><td>297</td></tr>
<tr><td>True -ve</td><td>2611</td><td>1338</td><td>1513</td><td>2898</td></tr>
<tr><td>Total relatives tested</td><td>4302</td><td>2675</td><td>2959</td><td>4681</td></tr>
</table>
*Probands where cascade testing was undertaken</td>
<td>Cascade testing of relatives of patients with DFH and PFH is cost-effective when using a combination of DNA testing for known family mutations and LDL-cholesterol levels in the remaining families.

The approach is more cost-effective than current primary prevention screening strategies.</td>
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Table 5.2. ICER of the DNA-based methods compared with each other cholesterol method for screening and identification of FH
<table>
<tr><th>Strategy</th><th>Cost</th><th>Effects (QALY)</th><th>Incremental cost</th><th>Incremental QALY</th><th>ICER (£/QALY)</th></tr>
<tr><td>Cholesterol</td><td>£44,576</td><td>10.89</td><td></td><td></td><td></td></tr>
<tr><td>DNA</td><td>£50,918</td><td>24.12</td><td>£6,341</td><td>13.23</td><td>£479</td></tr>
<tr><td>DNA+CholM-ve DFH</td><td>£52,670</td><td>24.28</td><td>-</td><td>-</td><td>ED*</td></tr>
<tr><td>DNA+CholM-ve DF+PFH</td><td>£54,799</td><td>25.18</td><td>33881</td><td>1.06</td><td>£3666</td></tr>
</table>
*Ruled out by extended dominance (ED)
CholM-ve, cascade testing using LDL-C in relatives of mutation-negative index cases

The DNA+DFH+PFH method was the most cost-effective cascade screening strategy. The ICER was estimated at £3666/QALY. Using this strategy, of the tested relatives 30.6% will be true positives, 6.3% false positives, 61.9% true negatives and 1.1% false negatives.

Probabilistic sensitivity analysis showed that this approach is 100% cost-effective using the conventional benchmark for cost-effective treatments in the NHS of between £20,000 and £30,000 per QALY gained.
</td>
<td></td>
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<tr>
<td>Marks 2000, UK[30]</td>
<td>A systematic review and cost-effectiveness analysis

The strategies that are considered are:
• Universal screening of school leavers at the age of 16 years</td>
<td>Clinical diagnosis strategies: For men, the most cost-effective strategy was case finding, identifying male relatives aged 16–24 years (£870 per LYG) and the least cost-effective was universal screening of males aged 45–54 years. For women, the most cost-effective strategy was case finding of the 35–44 year age group (£637 per LYG). The least cost-effective strategy for women was universal screening for those aged 45–54 years. Identifying 16 year olds in a</td>
<td>Case finding in the relatives of known FH patients is cost-effective, as is a screening strategy in young people, and screening of patients admitted to hospital with premature MI.</td>
</tr>
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<td>

Universal screening at the ages of 16–55 years
Opportunistic screening of people aged 16–55 years who visit their GP for another reason
Opportunistic screening of people who have been admitted to hospital with an early MI (aged 16–55 years)
Case finding of family members of an ‘index’ patient who has been identified with FH and is attending a lipid clinic

Outcome: Incremental cost per year of life gained
</td>
<td>
case-finding strategy is approximately three times more cost-effective than identifying them through a universal or opportunistic (GP) approach.
The pattern across the genetic diagnosis strategies was similar to that of clinical diagnosis. The exception is that universal (16) screening is no longer more cost-effective than case finding. The reason for this switch is because in strategies other than case finding, twice as many individuals now have to be invited for screening to find one case because a mutation can only be detected in 50% of cases.
Table 5.3. Comparison of the overall cost-effectiveness of clinical and genetic strategies
<table>
<tr><th>Strategy</th><th>Cost per LYG (clinical) (£)</th><th>Cost per LYG (genetic) (£)</th></tr>
<tr><td>Universal (16)</td><td>2,777</td><td>14,842</td></tr>
<tr><td>Universal</td><td>13,029</td><td>78,060</td></tr>
<tr><td>Opportunistic (GP)</td><td>11,310</td><td>70,009</td></tr>
<tr><td>Opportunistic (MI)</td><td>9,281</td><td>21,106</td></tr>
<tr><td>Case finding</td><td>3,097</td><td>3,300 (relatives only: proband with known mutation)
4,914 (cost of testing proband included)</td></tr>
</table>
</td>
<td>However, data on the effectiveness and cost implications of screening strategies is lacking, so it is difficult to conclude with certainty that one strategy is more effective or less costly than another.</td>
</tr>
</table>

Modifiable risk factors that can be used as proxy indicators for high cholesterol

Atherosclerosis Risk in Communities (ARIC) study in four US communities' tracked 15,792 adults aged 45-64 for an average period of 13.3 years (maximum 16.1 years). All participants were interviewed at baseline and were contacted annually and their hospital records were reviewed to identify whether there had been a CHD event (probable MI or definite CHD death). There were 932 CHD events and incident rates of CHD events per 1,000 person years and relative risk were calculated for smoking (former, current 1-14, current 15-29, current >30 cigarettes) against different bands of LDL-C [optimal LDL-C (<100 mg/dl); near/above optimal (100-129 mg/dl); borderline high (130-159 mg/di); high (160-189 mg/dl) and very high (≥190 mg/dl)] against having never smoked. Former smokers with optimal cholesterol levels risk was almost the same as if they never smoked RR 1.02 (0.59 -1.76) but increased across the bands. Generally relative risk increased with cigarette consumption for those with optimal cholesterol levels to RR 2.13 (0.98-4.61) for those who consumed >30 cigarettes. The same pattern was observed in other cholesterol level bandings.[31]

There were a number of studies on possible proxies for high cholesterol that were of interest but did not fully meet the inclusion criteria (Appendix D). These studies generally did not meet the age range criteria and included optimal cut-off values for predicting hypercholesterolemia in multi-ethnic populations,[32] the relative effects of obesity and insulin resistance on cardiovascular risk factors in nondiabetic and non-hypertensivemales,[33] cardiovascular mortality in overweight subjects,[34] waist circumference as a screening tool for cardiovascular risk factors,[35] correlation between waist circumference and ESC cardiovascular risk score,[36] waist to height ratio as screening tool,[37] and association of cigarette smoking and alcohol consumption[38] and association between eating competence and cardiovascular disease biomarkers[39].

Table 6. Overview of included studies relating to modifiable risk factors that can be used as proxy indicators for high cholesterol

<table>
<tr><th>Author, Date, Country</th><th>Study design</th><th>Findings</th><th>Conclusions, comment</th></tr>
<tr>
<td>Hozawa 2006[31]

USA</td>
<td>Prospective cohort

ARIC (Atherosclerosis Risk in Communities) study included 4 communities.

Baseline completed over period 1987-89. 15,792 participants aged between 45-64years were selected by list of area probability sampling. In one community only African-Americans were recruited.

Baseline interview - collected information on demographics, smoking and alcohol consumption, medication use, reproductive history and medical history and clinical examination (risk factors, cardiovascular conditions, ultrasound and ECG).

Participants were contacted annually and identified hospital records reviewed and those suggesting CHD were abstracted for validation.

Endpoint was CHD event defined as validated or probable MI or definite CHD death through to 31.12.2002.

All possible clinical CHD events were reviewed by ARIC Morbidity and Mortality classification committee using published criteria.</td>
<td>Over a mean duration of follow-up of 13.3 years (maximum 16.1years).
932 CHD events

Table 6.1. Incidents of CHD per 1,000 person year by cigarette consumption

<table>
<tr><th></th><th>Incidents CHD per 1,000 person-years</th></tr>
<tr><td>Current smokers</td><td>8.38</td></tr>
<tr><td>Former smokers</td><td>5.07</td></tr>
<tr><td>Never smoked</td><td>3.60</td></tr>
<tr><td>Optimal LDL-C (100 mg/dl)</td><td>3.28</td></tr>
<tr><td>Near/above optimal LDL-C (100-129 mg/dl)</td><td>4.16</td></tr>
<tr><td>Borderline high LDL-C (130-159 mg/dl)</td><td>5.10</td></tr>
<tr><td>High LDL-C (160-189 mg/dl)</td><td>7.04</td></tr>
<tr><td>Very high LDL-C (≥190 mg/dl)</td><td>9.38</td></tr>
</table>

Table 6.2. Relative risk of CHD event for smoking at different bandings of LDL-C

<table>
<tr><th></th><th>Optimal LDL-C (<100 mg/dl)</th><th>Borderline high LDL-C (130-159 mg/dl)</th><th>Very high LDL-C (≥190 mg/dl)</th></tr>
<tr><td>Former smoker</td><td>1.02 (0.59 -1.76)</td><td>1.19 (0.87-1.65)</td><td>1.12 (0.72-1.76)</td></tr>
<tr><td>Never smoked</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Current 1-14</td><td>1.84 (0.91-3.74)</td><td>1.76 (1.05-2.93)</td><td>2.07 (1.02-4.18)</td></tr>
<tr><td>Current 15-29</td><td>1.33 (0.66 -2.67)</td><td>2.91 (2.01-4.21)</td><td>2.25 (1.33-3.82)</td></tr>
<tr><td>Current 30+</td><td>2.13 (0.98-4.61)</td><td>3.80 (2.37-6.07)</td><td>3.80 (1.98-7.29)</td></tr>
<tr><td>Slope</td><td>1.23 (0.97-1.57)</td><td>1.61 (1.40-1.85)</td><td>1.53 (1.26-1.86)</td></tr>
</table>
</td>
<td>The authors conclude that their study shows a much higher risk CHD with heavy cigarette smoking in the prevalence of higher LDL-C than lower LDL-C, which reinforces the importance of smoking cessation in those with elevated cholesterol.</td>
</tr>
</table>

Discussions and conclusions

Is there evidence on the impact of restricting cholesterol testing within the NHS Check service, to those who are identified as being at a certain percentage risk of being diagnosed with CVD (10 year risk)?

AND

Is there evidence on the impact of restricting cholesterol testing within the NHS Check service, to those who are identified as being at a certain percentage risk of being diagnosed with CVD (lifetime risk)? If so, what is the impact of restricting cholesterol testing within the NHS Health Check service, to those who are identified as being at moderate or high risk of CVD in 10 year; and lifetime risk?

AND

If cholesterol testing is restricted, what is the optimal restriction to still ensure the health check is clinically effective for 10 year risk? What is the percentage risk that would be most effective? 10%? 20%? Or restriction to which specific population groups?

AND

If cholesterol testing is restricted, what is the optimal restriction to still ensure the health check is clinically effective for lifetime risk? What is the percentage risk that would be most effective? Or restriction to which specific population groups?

We found no direct evidence to answer these questions. There are partial insights into the impact of restricting cholesterol test from studies identified that compare the additional predictive value of using individualised cholesterol test results against age adjusted cholesterol population average values when using risk calculators. These studies, however, suggest that differences may be a result of how the risk calculators are structured and that age is the main risk factor in most equations. However, none of these studies were designed to answer questions on restricting the use of cholesterol testing in health checks.

We looked at local evaluations in the public domain of the implementation of NHS Health Checks to assess whether there had been any natural variations in the use of cholesterol testing that enable us to answer this question. However, the evaluation studies identified were mainly descriptive and formative in nature and provided no useful information or insights.

A secondary analysis of Health Survey for England data based on a PhD thesis was undertaken to estimate the sensitivity and specificity of a strategy of selective cholesterol testing (only if 10-year CVD risk is ≥10%). This found that, using the Framingham CVD equation to predict risk, specificity for identifying patients eligible for either antihypertensives or statins was 100% and sensitivity was 90% in individuals eligible for NHS Health Checks. This should be contextualised by the fact that in some areas >60% of NHS Health Checks attendees are at low 10-year CVD risk (<10%) and only 12% are high risk (≥20%). Furthermore of those at high risk the majority (75%) are not prescribed drugs.[40]

Our secondary analysis did not model strategies restricting cholesterol testing to patients at ≥12.5%, ≥15%, ≥20% 10-year CVD risk. Intuitively, restricting cholesterol testing to those at higher risk will reduce the costs of cholesterol testing but also reduce the number of eligible patients identified and treated. The optimum strategy therefore depends on the relative importance of costs in relation to benefits.

Cost-effectiveness modelling has been undertaken to determine the relationship between the additional costs and additional benefits of undertaking health checks in patients with estimated 10-year CVD risk ≥20%, ≥15%, ≥10%, ≥5%. However this is not restricted to cholesterol testing but compares the costs and benefits of inviting and offering a health check to patients at increasing risk.[41]

What would the impact of reducing cholesterol testing have on lifetime CVD prevention?

We included one study that reported on hazard ratios of different risk factors and CHD events. Lifetime CVD prevention would require individuals to agree and sustain lifestyle changes and adhere to medical interventions where indicated by their estimated CVD risk and our searches did not identify any study describing the use of cholesterol testing to support and sustain such changes.

Is there evidence to suggest that restricting cholesterol testing will change take up of the cardiovascular disease prevention programmes, specifically NHS health check?

AND

Is cholesterol testing a deciding factor in why people take up NHS health check?

There is no direct evidence on whether restricting cholesterol testing would affect take up of cardiovascular disease prevention programmes and none specifically on the NHS Health Checks. We found no specific research on whether cholesterol testing was a factor in the take up of NHS Health Checks. There was, however, some research on why individuals participate in cholesterol screening programmes. Research on population screening for high cholesterol has focused on educating the public to be aware of cholesterol, to know their cholesterol value and take personal ownership of avoiding the potential future health problems from high total cholesterol and LDC levels. It tended to show self-selection biases in community members who took part in such studies including higher prevalence of more health conscious and better educated individuals.

We identified qualitative studies, including evaluations of NHS Health Checks, that reported health professionals' attitudes to, and patients' experiences of health checks, but these studies did not specifically examine the role of cholesterol testing. There were two studies that made reference to patients requesting cholesterol testing as part of their health check and one of these studies suggested that cholesterol testing contributed to a more positive view by participants. While some GPs ranked cholesterol testing highly, others expressed concerns about unnecessary harm due to anxiety caused to patients receiving elevated results or false reassurance from favourable results.

Are there particular groups within the population that this decision would this disproportionally affect in terms of their likelihood to take up the initiative?

Again, we found no direct evidence. There was one study that indicated that woman faced barriers in undertaking cholesterol tests because CHD is stereotyped as being a man's disease.[42] While there are groups within the population that are less likely to take up the offer of a health check, further research is needed to determine whether restricting cholesterol testing would affect any specific group.

What would the impact of reducing cholesterol testing have on Familial Hypercholesterolaemia diagnosis?

Again, we found no direct evidence. Most of the available evidence on FH focused on the clinical and cost effectiveness of different diagnostic strategies in populations of a broad age range especially children and young adults. Population screening of cholesterol levels alone is not a cost effective approach for FH diagnoses and needs to be linked to genetic testing to confirm diagnosis of index cases before undertaking cascade screening of family members.

Our secondary analysis found that restricting cholesterol testing to patients at ≥10% risk would reduce the detection of patients with familial hypercholesterolaemia, particularly among younger patients.

How accurate is the QRisk 3 proxy cholesterol calculation for those who have not had a cholesterol test? For both 10 year risk and lifetime risk?

We found no studies that specifically mentioned QRisk3, so were unable to answer this question.

Is it possible to use modifiable risk factors for high cholesterol (tobacco use, alcohol, inactivity, weight, diet) as a proxy indicator to whether someone is likely to have high cholesterol? Could these behaviours be used as an additional risk factor as when to test for cholesterol? For both 10 year risk and lifetime risk

There has been research into the relationship between tobacco consumption and cholesterol levels showing that increased consumption evaluates cholesterol levels. We identified some studies that included a broader age range of participants (mainly younger population) that examined the association between BMI, waist circumference, waist to height and hip ratios, eating competence and alcohol consumption with cholesterol.

Conclusions

Limited analysis suggests that restricting cholesterol testing would have modest effects on the total numbers of patients identified as eligible for drug treatments. In younger people restrictive cholesterol testing is likely to significantly reduce the identification of the small number of individuals with familial hypercholesterolaemia.

There is insufficient evidence to predict the effects of cholesterol testing on uptake of NHS Health Checks.

The effect of restrictive testing on identification of patients eligible for drug treatments can be estimated accurately and different options explored by modelling using the QRisk equation.

Research recommendations

The reanalysis of Health Survey for England data illustrates that it is feasible to determine the number of individuals eligible for drug treatments and the proportion identified under a strategy of restrictive cholesterol testing. The most appropriate modelling would make use of electronic medical records from primary care and the QRisk equation. Electronic medical records from primary care accurately reflect both the mix of patients eligible for NHS Health Checks and the range of risk factor information available to general practices to identify patients for selective cholesterol testing. The QRisk equation is the CVD risk equation most widely in use in the UK to predict eligibility for treatment and its use is recommended in NICE guidelines. The analysis should consider equity effects of different selective cholesterol testing strategies by considering different effects on identification of patients by age, gender, deprivation banding and ethnicity. The analysis should consider a range of strategies for selective cholesterol testing in order to ensure that the optimum strategies are identified.

There is wide variation in uptake of NHS Health Checks between general practices (0% to 73%) and regions (9% to 31%)[43]. Unless the effects of selective cholesterol testing on uptake are very large the effects of other factors are likely to be more important. It is not possible to determine the effects of a strategy of selective cholesterol testing on uptake without undertaking empirical research comparing different strategies. However, the possible effects of a strategy of selective cholesterol testing on uptake of NHS Health Checks can be determined through survey of patients in the eligible population.

Appendix A: Main search strategy

Example search strategy for Ovid MEDLINE(R)

This strategy has been adapted for use in each of the other databases.

1 cardiovascular diseases/ or coronary disease/

2 cvd.ti,ab.

3 ((heart or cardiovascular or coronary) adj3 disease$).ti,ab.

4 or/1-3

5 (risk$ or likelihood or possibility or chance).mp. or prevent$.ti,ab.

6 exp risk/

7 or/5-6

8 health check$.ti,ab.

9 (diabetes adj3 screen$).ti,ab.

10 (cardiovascular adj3 screen$).ti,ab.

11 (population adj2 screen$).ti,ab.

12 (risk factor adj3 screen$).ti,ab.

13 (opportunistic adj3 screen$).ti,ab.

14 medical check$.ti,ab.

15 general check$.ti,ab.

16 periodic health exam$.ti,ab.

17 annual exam$.ti,ab.

18 annual review$.ti,ab.

19 NHSHC.ti,ab.

20 (NHS adj2 health check$).ti,ab.

21 or/8-20

22 4 and 7 and 21

Appendix B: Supplementary searches

B1. The Health Check strategy for Ovid MEDLINE(R) with specific qualitative filter

This strategy has been adapted for use in each of the other databases.

1 health check$.ti,ab.
2 (diabetes adj3 screen$).ti,ab.
3 (cardiovascular adj3 screen$).ti,ab.
4 (population adj2 screen$).ti,ab.
5 (risk factor adj3 screen$).ti,ab.
6 (opportunistic adj3 screen$).ti,ab.
7 medical check$.ti,ab.
8 general check$.ti,ab.
9 periodic health exam$.ti,ab.
10 annual exam$.ti,ab.
11 annual review$.ti,ab.
12 NHSHC.ti,ab.
13 (NHS adj2 health check$).ti,ab.
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 qualitative.tw.
16 themes.tw.
17 15 or 16
18 14 and 17

B2. The Cholesterol test strategy for Ovid MEDLINE(R) with specific qualitative filter

This strategy has been adapted for use in each of the other databases.

1 (Cholesterol adj5 test*).mp.

2 (Cholesterol adj5 screen*).mp.

3 (Hyperlipidemia adj5 test*).mp.

4 (hyperlipidemia adj5 screen*).mp.

5 (hypercholesterolemia adj5 test*).mp.

6 (hypercholesterolemia adj5 screen*).mp.

7 1 or 2 or 3 or 4 or 5 or 6

8 exp QUALITATIVE RESEARCH/

9 interview:.mp.

10 experience:.mp.

11 qualitative.tw.

12 8 or 9 or 10 or 11

13 7 and 12

14 Cholesterol/

15 diagnostic techniques, cardiovascular/ or mass screening/

16 exp Hyperlipidemias/

17 14 or 16

18 15 and 17

19 7 or 18

20 12 and 19

Appendix C: Excluded studies

C1. Main search (n=71)

ID	Reference	Excluded with reason
1304;	Assmann, G., H. Schulte, and P. Cullen, New and classical risk factors--the Munster heart study (PROCAM). European Journal of Medical Research, 1997. 2(6): p. 237-42.	This study reports on the recording of data collected by screening of adults aged 35-50 though GPs (35-30y) which included cholesterol testing.
1322;	Bartys, S., et al., Inequity in recording of risk in a local population-based screening programme for cardiovascular disease. European Journal of Cardiovascular Prevention & Rehabilitation, 2005. 12(1): p. 63-7.	This study reports that the recording of cholesterol is less complete for females, South East Asians and employed
1329	Bell K., A. Hayen, K. McGeechan, B. Neal and L. Irwig. Effects of additional blood pressure and lipid measurements on the prediction of cardiovascular risk. European Journal of Preventive Cardiology, 2012. 19(6): p. 1474-85.	This study looks at the inclusion of additional measurements of blood pressure.
1336;	Bhatnagar, D., Diagnosis and screening for familial hypercholesterolaemia: finding the patients, finding the genes. Annals of Clinical Biochemistry, 2006. 43(Pt 6): p. 441-56.	This paper was a narrative review.
1364;	Bush, T.L. and D. Riedel, Screening for total cholesterol. Do the National Cholesterol Education Program's recommendations detect individuals at high risk of coronary heart disease? Circulation, 1991. 83(4): p. 1287-93.	This paper was excluded as it did not mention risk scores and described an intervention which used lipid screening.
1366;	Cabrera M., M. A. Sanchez-Chaparro, P. Valdivielso, L. Prevalence of atherogenic dyslipidemia: association with risk factors and cardiovascular risk in Spanish working population. "ICARIA" study. Atherosclerosis, 2014. 235(2): p. 562-9.	This study was excluded because it was a prevalence study of atherogenic dyslipidaemia.
1374;	Chan W. K., A. Chiu, G. T. Ko. Ten-year cardiovascular risk in a Hong Kong population. Journal of Cardiovascular Risk, 1999. 6(3): p. 163-9.	This study was excluded because it was a prevalence study that involved calculating the percentage of Hong Kong population at risk based on screening programme using European Taskforce Coronary Risk Assessment which includes total cholesterol to calculate 10y risk.
1408;	De Backer G. G. New risk markers for cardiovascular prevention. Current Atherosclerosis Reports, 2014. 16(8): p. 427.	This study assessed the addition of HDL-C to SCORE equation which already includes cholesterol in calculating risk.
1422;	Ding X. H., P. Ye, X. N. Wang, et al The predictive value of baseline LDL-TG level on major adverse cardiovascular events in a	Described a routine health exam in China with 5 year follow-up. Reported on MACE not CV risk. and triglycerides not cholesterol.

	followed up cohort population. European Review for Medical & Pharmacological Sciences, 2017. 21(5): p. 1060-1064.	
1444;	Faeh, D., S. Rohrmann, and J. Braun, Better risk assessment with glycated hemoglobin instead of cholesterol in CVD risk prediction charts. European Journal of Epidemiology, 2013. 28(7): p. 551-5.	This study reports on use of glucose or glycated haemoglobin and patients had pre-existing disease.
1454;	Forster A. S., H. Dodhia, H. Booth, A. Dregan, et al.Estimating the yield of NHS Health Checks in England: a population-based cohort study. Journal of Public Health, 2015. 37(2): p. 234-40.	While this study provided insights into effects of treatment resulting from health checks, it provided no comparative evidence.
1465;	J Gander., X. Sui, L. J. Hazlett, B. Cai, J. R. Hebert and S. N. Blair. Factors related to coronary heart disease risk among men: validation of the Framingham Risk Score. Preventing Chronic Disease, 2014. 11: p. E140.	This study reports 10y risk for CHD using Framingham risk score in preventive medical exam with periodic visits by American patients (30-74y, 75% male, free of CHD/ cancer). Total cholesterol was measured but no comparative data provided.
1470;	Gharipour M., M. Sadeghi, M. Dianatkhah, P. Comparison between European and Iranian cutoff points of triglyceride/high-density lipoprotein cholesterol concentrations in predicting cardiovascular disease outcomes. Journal of Clinical Lipidology, 2016. 10(1): p. 143-9.	This study calculates the cut off for using cholesterol to detect increased CVD risk in Iranian population.
1489;	Grover S. A., M. Dorais and L. Coupal. Improving the prediction of cardiovascular risk: interaction between LDL and HDL cholesterol. Epidemiology, 2003. 14(3): p. 315-20.	Study population already had abnormal lipid levels. The study also did not provide any information on predictive value of including cholesterol testing.
1493;	Gustat J., A. Elkasabany, S. Srinivasan. Relation of abdominal height to cardiovascular risk factors in young adults: the Bogalusa heart study. American Journal of Epidemiology, 2000. 151(9): p. 885-91.	Age range of study population was 20-38y.
1507;	K Haralambos., S. D. Whatley, R. Edwards, R. et al Clinical experience of scoring criteria for Familial Hypercholesterolaemia (FH) genetic testing in Wales. Atherosclerosis, 2015. 240(1): p. 190-6.	Description of criteria for screening for genetic testing for familial hypercholesterolaemia for patients presenting at lipid clinics.
1515;	Hausenloy D. J., L. Opie and D. M. Yellon. Dissociating HDL cholesterol from cardiovascular risk. Lancet, 2010. 376(9738): p. 305-6.	Letter.
1516	Havas S., P. Greenland, R. Wones and B. Schucker. *Addressing unanswered questions about population cholesterol screenings: the Model Systems for Blood Cholesterol Screening Program.* American Journal of Preventive Medicine, 1989. **5**(6): p. 337-46.	Narrative review
1583	Jones A. F., J. Walker, C. Jewkes, F. L. Game, W. A. Bartlett, T. Marshall and G. R. Bayly. *Comparative accuracy of cardiovascular risk prediction methods in primary care patients.*	This study discusses the sensitivities of different risk tables, all of which total cholesterol.

	Heart, 2001. **85**(1): p. 37-43.	
1616;	B Kinosian., H. Glick and G. Garland. Cholesterol and coronary heart disease: predicting risks by levels and ratios. Annals of Internal Medicine, 1994. 121(9): p. 641-7.	This study compares total and LDL cholesterol and total cholesterol: HDL ratio and does not provide 10y risk.
1660;	Lee S. H. Characteristics and Vascular Complications of Familial Hypercholesterolemia in Korea. Journal of Atherosclerosis & Thrombosis, 2016. 23(5): p. 532-8.	Describes characteristics of patient with FH and their treatment.
1670	Li S. S., S. Pan, Y. T. Ma, et al Optimal cutoff of the waist-to-hip ratio for detecting cardiovascular risk factors among Han adults in Xinjiang. BMC Cardiovascular Disorders, 2014. 14: p. 93.	Population, this study reports on optimal waist to hip ration cut-off for detection of hypertension and dyslipidaemia in Chinese population aged >35 years (52 ± 12).
1691;	Mackowiak K., M. Nowicki, E. Wysocka, A. Brozek and L. Torlinski. [The impact of tobacco smoking on the selected risk factors for cardiovascular disease in students of Poznan University of Medical Sciences]. Przeglad Lekarski, 2012. 69(10): p. 819-23.	Young adults below the age range for HC. Polish (Abstract in English suggest smoking can modify plasma lipid profile)
1692	MacLean D. R., A. Petrasovits, P. W. Connelly, J. A. Little and B. O'Connor. Impact of different blood lipid evaluation and treatment guidelines on the proportion of Canadians identified and treated for elevated blood cholesterol. Canadian Heart Health Surveys Research Group. Canadian Journal of Cardiology, 1999. **15**(4): p. 445-51.	This study reports on differences between guidelines (but all appear to include cholesterol testing) for adults, aged 18-74y mixed population. Cholesterol was tested according to guidelines. Lower level of testing when Canadian guidelines are followed compared to when US guidelines are followed.
1705;	Marrugat J., J. Vila, J. M. Baena-Diez, M. Grau, J. Sala, R. Ramos, I. Subirana, M. Fito and R. Elosua. [Relative validity of the 10-year cardiovascular risk estimate in a population cohort of the REGICOR study]. Revista Espanola de Cardiologia, 2011. 64(5): p. 385-94.	Provides information on 10 year CVD risk (Framingham-based REGICOR) – includes cholesterol testing
1706	Marsh R. Cholesterol levels have negligible correlations with cardiovascular incidents. New Zealand Medical Journal, 2012. **125**(1364): p. 121-2.	Opinion
1724;	McGuire K. A., I. Janssen and R. Ross. Ability of physical activity to predict cardiovascular disease beyond commonly evaluated cardiometabolic risk factors. American Journal of Cardiology, 2009. 104(11): p. 1522-6	Study population (unhealthy population, USA)
1730	Menotti A., M. Lanti, P. E. Puddu, L. Carratelli, M. Mancini, M. Motolese, P. Prati and A. Zanchetti. The risk functions incorporated in Riscard 2002: a software for the prediction of cardiovascular risk in the general population based on Italian data. Italian Heart Journal: Official Journal of the Italian Federation of Cardiology, 2002. 3(2): p. 114-21.	This study provided information on the contribution of cholesterol to different models, but does not provide information on 10 year risk.

1732	Merry A. H., J. M. Boer, L. J. Schouten, T. Ambergen, E. W. Steyerberg, E. J. Feskens, W. M. Verschuren, A. P. Gorgels and P. A. van den Brandt. Risk prediction of incident coronary heart disease in The Netherlands: re-estimation and improvement of the SCORE risk function. European Journal of Preventive Cardiology, 2012. **19**(4): p. 840-8.	This study looks at changing predicators in SCORE, but does not remove cholesterol from the equation.
1733;	Meysamie A., S. Ghodsi, R. Ghalehtaki, A. Esteghamati, F. Asgari and M. M. Gouya; 2017	Prevalence of high-risk categories defined by C-reactive protein and risk score included cholesterol.
1764	Muir, L. A., George, P. M., Laurie, A. D., Reid, N., Whitehead, L. Preventing cardiovascular disease: a review of the effectiveness of identifying the people with familial hypercholesterolaemia in New Zealand. New Zealand Medical Journal, 2010. 123(1326):97-102.	This study focuses on mutation and cascade screening services to identify individuals with FH in New Zealand. The service is not within the remit of a health check.
1773;	Nakagami T., Q. Qiao, J. Tuomilehto, B. Balkau, N. Tajima, G. Hu and K. Borch-Johnsen. Distributions of High-Sensitivity C-Reactive Protein, Total Cholesterol-HDL Ratio and 10-Year Cardiovascular Risk: National Population-Based Study. Acta Medica Iranica, 2017. 55(4): p. 218-227.	Study reports on CVD mortality amongst a population free of CVD and diabetes, average follow-up was 5.9y. No mention of risk scores.
1830;	Paynter N. P. and N. R. Cook. Adding tests to risk based guidelines: evaluating improvements in prediction for an intermediate risk group. BMJ, 2016. 354: p. i4450	Methodology paper for how to assess the benefit of adding additional tests for patients in intermediate risk groups
1843;	Primdahl J., J. Clausen and K. Horslev-Petersen., Results from systematic screening for cardiovascular risk in outpatients with rheumatoid arthritis in accordance with the EULAR recommendations. Annals of the Rheumatic Diseases, 2013. 72(11): p. 1771-6.	Very specific population (patients with rheumatoid arthritis). Risk score includes cholesterol and does provide 10 year risk
1867;	Rodondi N., I. Locatelli, D. Aujesky, et al.Framingham risk score and alternatives for prediction of coronary heart disease in older adults. PLoS ONE [Electronic Resource], 2012. 7(3): p. e34287.	Population.2193 older adults outside Health Check age range without pre-existing CVD. Provides 8 year follow up data
1868;	Romanens M., F. Ackermann, J. D. Spence, R. et al. Improvement of cardiovascular risk prediction: time to review current knowledge, debates, and fundamentals on how to assess test characteristics. European Journal of Cardiovascular Prevention & Rehabilitation, 2010. 17(1): p. 18-23	Methodology paper
1917;	Serrano-Martinez M., E. Martinez-Losa, M. Prado-Santamaria, C. et al. To what extent are the effects of diet on coronary heart disease lipid-mediated? International Journal of Cardiology, 2004. 95(1): p. 35-8.	Population, this study provides information on the relationship between dietary fat and arthorogenic index in 139 patients who have had MI and no previous experience of vascular disease. Average age 61.9y (34-79) overlaps with Health Checks but the 139 included patients have had a MI.

1929;	Si S., J. R. Moss, T. R. Sullivan, S. S. Newton and N. P. Stocks. Effectiveness of general practice-based health checks: a systematic review and meta-analysis. British Journal of General Practice, 2014. 64(618): p. e47-53.	Systematic review of GP health checks in patients aged 35-65 looking at effectiveness of intervention but provides no information on CVD risk
1975;	Stitziel N. O., S. W. Fouchier, B. Sjouke, G. M, et al. Exome sequencing and directed clinical phenotyping diagnose cholesterol ester storage disease presenting as autosomal recessive hypercholesterolemia. Arteriosclerosis, Thrombosis & Vascular Biology, 2013. 33(12): p. 2909-14.	Irrelevant, should have been excluded at abstract.
2040;	Vrentzos G. E., J. A. Papadakis, E. S. Ganotakis, K. I. et al. Predicting coronary heart disease risk using the Framingham and PROCAM equations in dyslipidaemic patients without overt vascular disease. International Journal of Clinical Practice, 2007. 61(10): p. 1643-53.	Population this study looked at the differences in risk scores (Framingham vs PROCAM) in patients with or without family history and triglycerides in diagnosed dyslipidaemia patients without overt vascular disease.
2047;	Wallis E. J., L. E. Ramsay, I. Ul Haq, P. Ghahramani, et al.Coronary and cardiovascular risk estimation for primary prevention: validation of a new Sheffield table in the 1995 Scottish health survey population.[Erratum appears in BMJ 2000 Apr 15;320(7241):1034]. BMJ, 2000. **320**(7236): p. 671-6.	This study describes the use of total:HDL ratios in estimating coronary and cardiovascular risk using 1995 Scottish Health Survey population to validate revisions to the Sheffield Table. Age range 38-5-64 overlaps with health checks
2065;	Wierzbicki A. S. Cardiovascular screening: which populations, what measures of risk? International Journal of Clinical Practice, 2011. 65(1): p. 3-5.	Opinion
2066;	Wierzbicki A. S., P. J. Twomey and T. M. ReynoldsScreening for cardiovascular disease. European Heart Journal, 2004. 25(11): p. 996; author reply 996-7.	Opinion
2070;	Wilson P. W.Lipoprotein measurements--setting priorities. American Journal of Medicine, 2001. 110(1): p. 71-2.	Opinion
2071;	Wilson S., A. Johnston, J. Robson, N. R. Poulter, D. J. Collier, G. S. Feder and M. J. Caulfield. Predicting coronary risk in the general population--is it necessary to measure high-density lipoprotein cholesterol? Journal of Cardiovascular Risk, 2003. **10**(2): p. 137-41.	This study reports use of average values in the absence of cholesterol test value data. It assumed 1 mmol/l HDL in absence of data and compared Joint British Society charts and Framingham. Mean age 50 ± 10, CV free, no hypertension or cholesterol treatment.
2113;	Artac M., A. R. H. Dalton, A. Majeed, K. Huckvale, J. Car, C. Graley and C. Millett. Assessment of cardiovascular risk factors prior to NHS Health Checks in an urban SETTING: cross-sectional study. JRSM Short Reports, 2012. 3(3): p. 17.	While this study looks at CVD risks in NHS health checks it is only concerned with the extent to which they are recorded in patient records

2119;	Bhopal R. S., R. W. Humphry and C. M. Fischbacher. Changes in cardiovascular risk factors in relation to increasing ethnic inequalities in cardiovascular mortality: comparison of cross-sectional data in the Health Surveys for England 1999 and 2004. BMJ Open, 2013. 3(9): p. e003485.	This study looks at the changes in overtime in risk between different ethnic groups. It provides information on percentage change within group including HDL and total cholesterol but does provide information on absolute risk.
2140;	Dachsel M. and E. Lee. Opportunistic health checks in a retail environment. London Journal of Primary Care, 2011. 4(1): p. 5-10.	Study does not mention cholesterol
2149;	El-Osta A., M. Woringer, E. Pizzo, T. Verhoef, C. Dickie, M. Z. Ni, J. R. Huddy, M. Soljak, G. B. Hanna and A. Majeed. Does use of point-of-care testing improve cost-effectiveness of the NHS Health Check programme in the primary care setting? A cost-minimisation analysis. BMJ Open, 2017. 7(8): p. e015494.	Looks at the use of point of care testing to improve cost-effectiveness of NHS health checks. No information on the impact of removing cholesterol testing but does provide information cost of tests.
2160;	Geue, C. J. D. Lewsey, D. F. MacKay, G. Antony, C. M. Fischbacher, J. Muirie and G. McCartney. Does use of point-of-care testing improve cost-effectiveness of the NHS Health Check programme in the primary care setting? A cost-minimisation analysis. BMJ Open, 2017. 7(8): p. e015494.	This study is an analysis of Scottish Keep Well health check programme and does not provide information on cholesterol testing.
2169;	Hardy S., K. Deane and R. Gray. The Northampton Physical Health and Wellbeing Project: the views of patients with severe mental illness about their physical health check. Mental Health in Family Medicine, 2012. **9**(4): p. 233-40	Population, very small population (n=5). Different age groups. GP health checks – does not mention cholesterol
2178;	Holland C., Y. Cooper, R. Shaw, H. Pattison and R. Cooke. Effectiveness and uptake of screening programmes for coronary heart disease and diabetes: a realist review of design components used in interventions. BMJ Open, 2013. 3(11): p. e003428.	Realist review of uptake and effectiveness of screening programmes. Knowledge of cholesterol levels can affect dietary changes. Does not report on risk levels
2184;	Hua X., R. McDermott, T. Lung, M. Wenitong, A. Tran-Duy, M. Li and P. Clarke. Validation and recalibration of the Framingham cardiovascular disease risk models in an Australian Indigenous cohort. European Journal of Preventive Cardiology, 2017. 24(15): p. 1660-1669.	Population, well person check in indigenous population not directly comparable. Found Framingham score underestimated risk.
2191;	Kato M. M., M. B. Currier, O. Villaverde and M. Gonzalez-Blanco. The relation between body fat distribution and cardiovascular risk factors in patients with schizophrenia: a cross-sectional pilot study. Primary Care Companion to the Journal of Clinical Psychiatry, 2005. **7**(3): p. 115-8; quiz 119-20.	Population, this study looks at the relationship between abnormal waist circumference and dyslipidaemia in patients with schizophrenia aged 20-73 years.
2230;	Mytton O. T., C. Jackson, A. Steinacher, A. Goodman, C. Langenberg, S. Griffin, N. Wareham and J. Woodcock. The current and potential health benefits of the National Health Service Health Check cardiovascular	Modelling study of NHS health checks which does not look at the use of cholesterol testing.

	disease prevention programme in England: A microsimulation study. PLoS Medicine / Public Library of Science, 2018. 15(3): p. e1002517.	
2268;	Serrano A., V. Pascual and D. Grupo.[Opinion from physicians on the need for dyslipidemia screening in cardiovascular risk. Similarities and differences between primary care and other specialties. The DIANA study]. Semergen Sociedad Espanola de Medicina Rural y Generalista, 2017. **43**(7): p. 486-492.	This study describes Spanish physicians' views on dyslipidaemia screening.
2284;	Thio S. L., T. B. Twickler, M. J. Cramer and P. Giral. National differences in screening programmes for cardiovascular risks could obstruct understanding of cardiovascular prevention studies in Europe. Netherlands Heart Journal, 2011. 19(11): p. 458-63.	This study compares screening programmes in France and Netherlands. Provides information on lipid profiles but no useful information on the importance of cholesterol testing on CVD risk.
2887;	de Backer G., M. Kornitzer, M. Dramaix, J. et al. HDL cholesterol and coronary risk. [French]. Annales de Cardiologie et d'Angeiologie, 1980. **29**(6): p. 431-437.	This study reports on 40-55 year old men who receive CV screening and have their HDL levels measured. Does not calculate CVD risk.
2313;	Woringer M., J. J. Nielsen, L. Zibarras, J. Evason, A. P. Kassianos, M. Harris, A. Majeed and M. Soljak. Development of a questionnaire to evaluate patients' awareness of cardiovascular disease risk in England's National Health Service Health Check preventive cardiovascular programme. BMJ Open, 2017. 7(9): p. e014413.	Methodology. Development of a psychometric instrument.
2317;	Yoo C. S., K. Lee, S. H. Yi, J.-S. Kim and H.-C. Kim., Association of heart rate variability with the framingham risk score in healthy adults. Korean Journal of Family Medicine, 2011. 32(6): p. 334-40.	This study looks at the relationship between heart rate variability and Framingham in healthy Korean adults. Does not provide information on risk levels.
2391	Mortensen M. B., S. Afzal, B. G. Nordestgaard and E. Falk. The high-density lipoprotein-adjusted SCORE model worsens SCORE-based risk classification in a contemporary population of 30 824 Europeans: The Copenhagen General Population Study. European Heart Journal, 2015. **36**(36): p. 2446-2453.	This study describes the addition of HDL to SCORE which already includes total cholesterol.
2423;	Kirke A. B., R. A. Barbour, S. Burrows, et al. Systematic detection of familial hypercholesterolaemia in primary health care: A community based prospective study of three methods. Heart Lung and Circulation, 2015. 24(3): p. 250-256.	This study compares three different case finding methods
2559	Kirke, A., Watts, G. F., Emery, J. Detecting familial hypercholesterolaemia in general practice. Australian Family Physician, 2012. 41(12):965-968.	A narrative review outlining the different strategies used in general practice for detecting FH.

2698;	Yu J. M., D. Y. Hu, Y. H. Sun and Q. W. Jiang. The China physicians' cardiovascular risk evaluation and prevention of cardiovascular events (care) survey: A multicenter, prospective, cohort analysis of physicians' risks and awareness of assessment models. Circulation, 2010. 122 (2): p. e81-e82.	This study is a survey of physicians' awareness of CVD risk estimation. Abstract form only
2926;	Amor A. J., M. Serra-Mir, M. A. Martinez-Gonzalez. Prediction of Cardiovascular Disease by the Framingham-REGICOR Equation in the High-Risk PREDIMED Cohort: Impact of the Mediterranean Diet Across Different Risk Strata. Journal of the American Heart Association, 2017. 6(3).	Population, study inclusion criteria included type2 diabetes or 3 CVR factors for diet intervention
2955;	Bakker, L. E. H. M. R. Boon, W. Annema, A. et HDL functionality in South Asians as compared to white Caucasians. Nutrition Metabolism and Cardiovascular Diseases, 2016. 26(8): p. 697-705.	Population, this study looks at HDL functionality in neonates, adolescents and adults.
3030	da Silva IT, de Almeida-Pititto B, Ferreira SRG. Reassessing lipid metabolism and its potentialities in the prediction of cardiovascular risk. Arquivos Brasileiros De Endocrinologia E Metabologia. 2015;59(2):171-80.	This study was a narrative review on different lipid markers
3156;	Harari G., M. S. Green, A. Magid and S. Zelber-Sagi. Usefulness of Non-High-Density Lipoprotein Cholesterol as a Predictor of Cardiovascular Disease Mortality in Men in 22-Year Follow-Up. American Journal of Cardiology, 2017. 119(8): p. 1193-1198.	This study was a 22y follow-up of males in employee screening programme and does not specifically answer any of the questions.
3203;	Jain A., R. Puri and D. R. Nair; 2017 South Asians: why are they at a higher risk for cardiovascular disease? Current Opinion in Cardiology, 2017. 32(4): p. 430-436.	This study was a narrative review.
3441;	Rabanal K. S., H. E. Meyer, G. S. Tell, et al. Can traditional risk factors explain the higher risk of cardiovascular disease in South Asians compared to Europeans in Norway and New Zealand? Two cohort studies. BMJ Open, 2017. 7(12).	While the study suggest that differences in CVD risk can be explained by differences in Total cholesterol / HDL and diabetes, does not provide information on the impact of reducing cholesterol testing. PREDICT software for CVD risk management in Primary Care.
3443;	Ramezankhani A., F. Bagherzadeh-Khiabani, D. Khalili, F. et al. A new look at risk patterns related to coronary heart disease incidence using survival tree analysis: 12 Years Longitudinal Study. Scientific Reports, 2017. 7.	This study reports on predictors for CHD, no comparisons of with and without cholesterol. 12y longitudinal study in Iran with analysis using survival tree analysis.

C2. Qualitative searches and Health Checks (n=19)

ID	Reference	Excluded with reason
Q298	Ahmad, F., et al. Perspectives of family physicians on computer-assisted health-risk assessments. Journal of Medical Internet Research, 2010. 12(2):e12.	This study reports on psychosocial health risks and does not concentrate on CVD risk; no specific references to cholesterol testing.
Q305	Ampt, A.J., et al. Attitudes, norms and controls influencing lifestyle risk factor management in general practice. BMC Family Practice, 2009. 10:59.	This study focuses on lifestyle interventions.
Q335	Broholm-Jorgensen, M., et al. Balancing trust and power: a qualitative study of GPs perceptions and strategies for retaining patients in preventive health checks. Scandinavian Journal of Primary Health Care, 2017. 35(1):89-97.	There were no specific references to cholesterol testing.
Q337	Burgess, C., et al. Influences on individuals' decisions to take up the offer of a health check: a qualitative study. Health Expectations, 2015. 18(6):2437-48.	There were no specific references to cholesterol testing.
Q342	Cheong, A.T., et al. Determinants for cardiovascular disease health check questionnaire: A validation study. PLoS ONE [Electronic Resource], 2017. 12(11): e0188259.	Validation of psychometric properties of questionnaire which has no items on cholesterol.
Q343	Cheong, A.T., et al. To Check or Not to Check? A Qualitative Study on How the Public Decides on Health Checks for Cardiovascular Disease Prevention.[Erratum appears in PLoS One. 2016;11(8):e0162152; PMID: 27560186]. PLoS ONE [Electronic Resource], 2016. 11(7):e0159438	There were no specific references to cholesterol testing.
Q393	Groenenberg, I., et al. 'Check it out!' Decision-making of vulnerable groups about participation in a two-stage cardiometabolic health check: a qualitative study. Patient Education & Counseling, 2015. 98(2):234-44.	There were no specific references to cholesterol testing.
Q535	Shaw, R.L., et al. GPs' perspectives on managing the NHS Health Check in primary care: a qualitative evaluation of implementation in one area of England. BMJ Open, 2016. 6(7): e010951.	There were no specific references to cholesterol testing.

Q536	Shaw, R.L., et al. Be SMART: examining the experience of implementing the NHS Health Check in UK primary care. BMC Family Practice, 2015. 16:1.	Focus of study was dietary changes; no specific references to cholesterol testing.
Q540	Sinclair, A. and H.A. Alexander. Using outreach to involve the hard-to-reach in a health check: what difference does it make? Public Health, 2012. 126(2):87-95.	There were no specific references to cholesterol testing.
Q551	Sutkowi-Hemstreet, A., et al. Adult Patients' Perspectives on the Benefits and Harms of Overused Screening Tests: a Qualitative Study. Journal of General Internal Medicine, 2015. 30(11):1618-26.	There were no specific references to cholesterol testing.
Q564	Usher-Smith, J. A., et al. Patient experience of NHS health checks: a systematic review and qualitative synthesis. BMJ Open, 2017. 7(8): e017169	Systematic review with some potentially relevant qualitative studies. References were checked and one primary study identified (Strutt E. et al, 2011; Thesis).
Q590	Baker, C., et al. Patients' perceptions of a NHS Health Check in the primary care setting. Quality in Primary Care, 2014. 22(5):232-237.	Study identified from main searches and was already included in this systematic review.
Q599	Ellis, N., et al. A qualitative investigation of non-response in NHS health checks. Archives of Public Health, 2015. 73(1):14.	There were no specific references to cholesterol testing.
Q606	Harte, E., et al. Reasons why people do not attend NHS Health Checks: a systematic review and qualitative synthesis. British Journal of General Practice, 2018. 68(666): e28-e35.	Systematic review with some potentially relevant qualitative studies. References were checked for identification of primary studies. The study itself does not mention cholesterol testing.
Q620	Mills, K., et al. Views of commissioners, managers and healthcare professionals on the NHS Health Check programme: a systematic review. BMJ Open, 2017. 7(11): e018606.	Systematic review with some potentially relevant qualitative studies. References were checked for identification of primary studies. The study itself does not mention cholesterol testing.
Q769	Baker, C., et al. Perceptions of health professionals involved in a NHS Health Check care pathway. Practice Nursing, 2015. 26(12):608-612	This study focuses on Health Checks implementation; no specific references to cholesterol testing.
Q789	Drennan, V. Barriers and reasons for failing to attend NHS health checks. Primary Health Care, 2015. 25(4): 15-15.	There were no specific references to cholesterol testing.
Q795	Kirby, M. and I. Machen. Impact on clinical practice of the Joint British Societies' cardiovascular risk assessment tools.	There were no specific references to cholesterol testing.

	International Journal of Clinical Practice, 2009. 63(12): 1683-1692.	

C3. Qualitative searches and cholesterol testing (n=12)

ID	Reference	Excluded with reason
QC16	Backer, E. L., Gregory, P., Jaen, C. R., Crabtree, B. F. A closer look at adult female health care maintenance visits. Family Medicine, 2006. 38(5):355-360.	Intervention was not equivalent to Health Checks (age over 19 years). US study.
QC19	Bankhead, C. R., Brett, J., Bukach, C., Webster, P., Stewart-Brown, S., Munafo, M., Austoker, J. The impact of screening on future health-promoting behaviours and health beliefs: a systematic review. Health Technology Assessment, 2003. 7(42):1-92.	Overarching review of screening for a number of conditions including high cholesterol but not equivalent to Health Checks.
QC64	Defesche. J.C. Defining the challenges of FH screening for familial hypercholesterolemia. Journal of Clinical Lipidology, 2010. 4(5):338-341.	Overview and opinion piece. Identifying FH patients of all ages.
QC65	Deskins, S., Harris, C. V., Bradlyn, A. S., Cottrell, L., Coffman, J. W., Olexa, J., Neal, W. Preventive care in Appalachia: use of the theory of planned behavior to identify barriers to participation in cholesterol screenings among West Virginians. Journal of Rural Health, 2006. 22(4):367-374.	The study's focus was on why members of a community in North America would take up the opportunity for screening for high cholesterol. A school-based programme.
Q69	Emmelin, M., Weinehall, L., Stenlund, H., Wall, S., Dahlgren, L. To be seen, confirmed and involved--a ten year follow-up of perceived health and cardiovascular risk factors in a Swedish community intervention programme. BMC Public Health, 2007. 7:190.	An intervention programme mainly to evaluate risk factor reduction (including cholesterol) and overall perceived health.
QC101	Hardcastle, S. J., Legge, E., Laundy, C. S., Egan, S. J., French, R., Watts, G. F., Hagger, M. S. Patients' perceptions and experiences of familial hypercholesterolemia, cascade genetic screening and treatment. International Journal of Behavioral Medicine, 2015. 22(1):92-100.	This study focuses on genetically diagnosed FH patients (age over 18 years) and their experiences mainly on cholesterol treatment. No specific reference to Health Checks.
QC106	Heath, G. W., Fuchs, R., Croft, J. B., Temple, S. P., Wheeler, F. C. Changes in blood cholesterol awareness: final results from the South Carolina Cardiovascular Disease Prevention Project. American Journal of Preventive Medicine, 1995. 11(3):190-196.	This study focuses on changes in blood cholesterol awareness following a community-based intervention. No specific reference to Health Checks.

QC301	Hallowell, N., Jenkins, N., Douglas, M., Walker, S., Finnie, R., Porteous, M., Lawton, J. Patients' experiences and views of cascade screening for familial hypercholesterolemia (FH): a qualitative study. Journal of Community Genetics, 2011. 2(4):249-257.	This study focuses on the views of FH patients (age ≤45 years) of genetic screening. No specific reference to Health Checks.
QC334	Petrova, D., Garcia-Retamero, R., Catena, A. Lonely hearts don't get checked: On the role of social support in screening for cardiovascular risk. Preventive Medicine, 2015. 81:202-208.	This study uses data from the Spanish national health survey to look at factors that affected the likelihood of being screened for cholesterol in the past 12 months.
Q133	Klepp, K. I., Matthiesen, S. B., Ulvik, R. J., Aaro, L. E. The Norwegian cholesterol campaign: a one year follow-up evaluation of a local action. Homeostasis in Health & Disease, 1991. 33(5-6):239-245.	Full text not available
Q202	Purchase, S., Vickery, A., Garton-Smith, J., O'Leary, P., Sullivan, D., Slattery, M., Playford, D., Watts, G. A framework for bridging the gap in the care of familial hypercholesterolaemia in the community: pragmatic and economic perspectives. International Journal of Evidence-Based Healthcare, 2014. 12(4):244-254.	Full text not available
Q249	Stockbridge, H., Hardy, R. I., Glueck, C. J. Public cholesterol screening: motivation for participation, follow-up outcome, self-knowledge, and coronary heart disease risk factor intervention. Journal of Laboratory & Clinical Medicine, 1989. 114(2):142-151.	Full text not available

Appendix D: Studies kept aside

Ref no	Authors date	Reason for being kept a side
1302;	Ashwell, M. and Gibson, S. Waist to height ratio is a simple and effective obesity screening tool for cardiovascular risk FACTORS: Analysis of data from the British National Diet And Nutrition Survey of adults aged 19-64 years. Obesity Facts, 2009. 2(2):97-103.	**Keep aside (Q12):** This study reports on the waist to height ratio association with CVD risk factors including cholesterol. However, age range of the population is younger than health checks.
1382;	Cheong, K. C., Ghazali, S. M., Hock, L. K., Yusoff, A. F., Selvarajah, S., Haniff, J., Zainuddin, A. A., Ying, C. Y., Lin, K. G., Rahman, J. A., Shahar, S., Mustafa, A. N. Optimal waist circumference cut-off values for predicting cardiovascular risk factors in a multi-ethnic Malaysian population. Obesity	**Keep aside (Q12):** This study reports on the relationship between waist circumference and diabetes, hypertension and hypercholesterolemia in South East Asian population.

	Research & Clinical Practice, 2014. 8(2):e154-162.	
1383;	Cheong, K. C., Yusoff, A. F., Ghazali, S. M., Lim, K. H., Selvarajah, S., Haniff, J., Khor, G. L., Shahar, S., Rahman, J. A., Zainuddin, A. A., Mustafa, A. N. Optimal BMI cut-off values for predicting diabetes, hypertension and hypercholesterolaemia in a multi-ethnic population. Public Health Nutrition, 2013. 16(3):453-459.	**Keep aside (Q12):** Same as 1382
93	Goldman, R. E., Parker, D. R., Eaton, C. B., Borkan, J. M., Gramling, R., Cover, R. T., Ahern, D. K. Patients' perceptions of cholesterol, cardiovascular disease risk, and risk communication strategies.[Erratum appears in Ann Fam Med. 2006 Jul-Aug;4(4):371]. Annals of Family Medicine, 2006. 4(3): 205-12.	**Keep aside (Q6/7):** This study has a broader research aim looking at patients' perceptions of cholesterol and CVD risk and their reactions to 3 strategies for communicating CVD risk.
1478	Godsland, I. F., Leyva, F., Walton, C., Worthington, M., Stevenson, J. C. Associations of smoking, alcohol and physical activity with risk factors for coronary heart disease and diabetes in the first follow-up cohort of the Heart Disease and Diabetes Risk Indicators in a Screened Cohort study (HDDRISC-1). Journal of Internal Medicine, 1998. 244(1):33-41.	**Keep aside (Q12):** This study examines the associations of smoking, alcohol and physical activity with total and HDL cholesterol.
1504;	Han, T. S., van Leer, E. M., Seidell, J. C., Lean, M. E. Waist circumference as a screening tool for cardiovascular risk FACTORS: evaluation of receiver operating characteristics (ROC). Obesity Research, 1996. 4(6): 533-547.	**Keep aside (Q12):** This study reports on the relationship between waist circumference and high cholesterol, low HDL cholesterol and hypertension.
1708;	Marti, B., Dai, S., Rickenbach, M., Wietlisbach, V., Bucher, C., Barazzoni, F., Gutzwiller, F. [Total cholesterol, HDL-cholesterol and blood pressure in relation to life style: results of the first population screening of the Swiss MONIKA Project]. Journal Suisse de Medecine, 1990. 120(51-52):1976-1988.	**Keep aside (Q12):** This study reports on the association of modifiable lifestyle factors with serum cholesterol and blood pressure
1764;	Muir, L. A., George, P. M., Laurie, A. D., Reid, N., Whitehead, L. Preventing cardiovascular disease: a review of the effectiveness of identifying the people with familial hypercholesterolaemia in New Zealand. New Zealand Medical Journal, 2010. 123(1326):97-102.	**Keep aside (Q9):** This study provides background on cascade screening.
1792;	Nye, E. R., Lithell, H., Mann, J. I. Risk factors for coronary heart disease in New Zealand and Sweden: Dunedin and Uppsala compared. New Zealand Medical Journal, 1991. 104(916): 305-307.	**Keep aside (Q12):** This study reports on correlation between waist: hip ratio and BMI and cholesterol levels (total and HDL, and triglycerides) in two populations.
1826	Park, S. H., Lee, W. Y., Lee, Y. S., Rhee, E. J., Kim, S. W. The relative effects of obesity and	**Keep aside (Q12):** This study reports on the relative effects of obesity (BMI) on total and LDL cholesterol

	insulin resistance on cardiovascular risk factors in nondiabetic and normotensive men. Korean Journal of Internal Medicine, 2004. 19(2):75-80.	and waist circumference.
1845	Psota, T. L., Lohse, B., West, S. G. Associations between eating competence and cardiovascular disease biomarkers. Journal of Nutrition Education & Behavior, 39(5Suppl):S171-178.	**Keep aside (Q12):** This study investigates the relationship between eating competence and HDL cholesterol testing. No CV risks.
1847;	Rabindranath K. S., N. R. Anderson, R. Gama and M. R. Holland., Comparative evaluation of the new Sheffield table and the modified joint British societies coronary risk prediction chart against a laboratory based risk score calculation. Postgraduate Medical Journal, 2002. **78**(919): p. 269-72.	**Keep a side (Q1-5):** This study compares Sheffield table against JBS. It reports on 10y CHD risk and appears to involve cholesterol in calculations. It suggests a potential 13.4% reduction in requests for screening.
1906;	Schunkert, H., Moebus, S., Hanisch, J., Bramlage, P., Steinhagen-Thiessen, E., Hauner, H., Weil, J., Wasem, J., Jockel, K. H. The correlation between waist circumference and ESC cardiovascular risk score: data from the German metabolic and cardiovascular risk project (GEMCAS). Clinical Research in Cardiology, 2008. 97(11):827-835.	**Keep aside (Q12):** This study reports a correlation between waist circumference and cholesterol, but found all risk factors increase with waist circumference.
2004;	Thomas, F., Bean, K., Pannier, B., Oppert, J. M., Guize, L., Benetos, A. Cardiovascular mortality in overweight subjects: the key role of associated risk factors. Hypertension, 2005. 46(4): 654-659.	**Keep aside (Q12):** Reports on association in the absence of hypertension between BMI at baseline with hypercholesterolemia.
2007;	Tian, H. G., Nan, Y., Liang, X. Q., Yang, X. L., Shao, R. C., Pietinen, P., Nissinen, A. Relationship between serum lipids and dietary and non-dietary factors in a Chinese population. European Journal of Clinical Nutrition, 1995. 49(12): 871-882.	**Keep aside (Q12):** Reports on the association between alcohol and BMI with total cholesterol in Chinese population (15-64y (subgroups available)0.
2115;	Baker, C., Loughren, E. A., Crone, D., Kallfa, N. Patients' perceptions of a NHS Health Check in the primary care setting. Quality in Primary Care, 2014. 22(5):232-237.	**Keep aside (Q6/7):** This qualitative study reports on patient's perceptions of NHS health checks. There is one quote on cholesterol.
2824;	Lee, K. S., Park, C. Y., Meng, K. H., Bush, A., Lee, S. H., Lee, W. C., Koo, J. W., Chung, C. K. The association of cigarette smoking and alcohol consumption with other cardiovascular risk factors in men from Seoul, Korea. Annals of Epidemiology, 1998. 8(1):31-38.	**Keep aside (Q12):** This study reports on Korean males aged 20+years receiving a health exam and the effects of smoking and alcohol on risk factors including cholesterol.
3001;	Catapano, A. L., Wiklund, O., European Atherosclerosis Society. Think Again About Cholesterol Survey. Atherosclerosis Supplements, 2015. 20:1-5.	**Keep aside (Q6/7):** This study is a population survey about cholesterol and CVD (age 25+y) in 11 EU countries.
QC82	Frich, J. C., Malterud, K., Fugelli, P. Women at risk of coronary heart disease experience barriers to diagnosis and treatment: a qualitative interview study. Scandinavian	**Keep aside (Q9):** This study explores the barriers to diagnosis of FH in women at risk.

	Journal of Primary Health Care, 2006. 24(1):38-43.	
QC267	van den Nieuwenhoff, H. W., Mesters, I., de Vries, N. K. Public awareness of the existence of inherited high cholesterol. European Journal of Cardiovascular Prevention & Rehabilitation, 2006. 13(6):990-992.	**Keep aside (Q9):** This study explores public awareness of the existence of hereditary lipid disorders such as FH.

References

1. Usher-Smith JA, Harte E, MacLure C, et al. Patient experience of NHS health checks: a systematic review and qualitative synthesis. *BMJ Open* 2017;7(8):e017169. doi: 10.1136/bmjopen-2017-017169 [published Online First: 2017/08/13]

2. Robson J, Dostal I, Sheikh A, et al. The NHS Health Check in England: an evaluation of the first 4 years. *Bmj Open* 2016;6(1) doi: ARTN e008840.10.1136/bmjopen-2015-008840

3. K.C.M. C. National Evaluation of the NHS Health Check Programme. Imperial College London, 2016.

4. Allan GM, Nouri F, Korownyk C, et al. Variation among cardiovascular risk calculators in relative risk increases with identical risk factor increases. *BMC Res Notes* 2015;8:417. doi: 10.1186/s13104-015-1401-8 [published Online First: 2015/09/09]

5. Hippisley-Cox J, Coupland C, Robson J, et al. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. *BMJ* 2010;341:c6624. doi: 10.1136/bmj.c6624 [published Online First: 2010/12/15]

6. Cooper JA, Miller GJ, Humphries SE. A comparison of the PROCAM and Framingham point-scoring systems for estimation of individual risk of coronary heart disease in the Second Northwick Park Heart Study. *Atherosclerosis* 2005;181(1):93-100.

7. Karmali KN, Goff DC, Jr., Ning H, et al. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. *Journal of the American College of Cardiology* 2014;64(10):959-68.

8. Anderson KM, Odell PM, Wilson PW, et al. Cardiovascular disease risk profiles. *Am Heart J* 1991;121(1 Pt 2):293-8. [published Online First: 1991/01/01]

9. [CG127] NCg. Hypertension in adults: diagnosis and management, 2011.

10. [CG181] NCg. Cardiovascular disease: risk assessment and reduction, including lipid modification. 2014 doi: https://www.nice.org.uk/guidance/cg181

11. Harris RE, Backlund JY, Haley NJ, et al. Population screening for plasma cholesterol: community-based results from Atlanta. *Southern Medical Journal* 1989a;82(11):1370-6.

12. Harris RE, Haley NJ, Muscat JE, et al. Population screening for plasma cholesterol: community-based results from Miami. *Journal of the Florida Medical Association* 1989b;76(10):853-60.

13. Wynder EL, Harris RE, Haley NJ. Population screening for plasma cholesterol: community-based results from Connecticut. *American Heart Journal* 1989;117(3):649-56.

14. Ismail H, Atkin K. The NHS Health Check programme: insights from a qualitative study of patients. *Health Expectations* 2016;19(2):345-55.

15. Ismail H, Kelly S. Lessons learned from England's Health Checks Programme: using qualitative research to identify and share best practice. *BMC Family Practice* 2015;16:144.

16. Jenkinson CE, Asprey A, Clark CE, et al. Patients' willingness to attend the NHS cardiovascular health checks in primary care: a qualitative interview study. *BMC Family Practice* 2015;16:33.

17. Perry C, Thurston M, Alford S, et al. The NHS health check programme in England: a qualitative study. *Health Promotion International* 2014;31(1):106-15.

18. Riley R, Coghill N, Montgomery A, et al. Experiences of patients and healthcare professionals of NHS cardiovascular health checks: a qualitative study. *Journal of Public Health* 2016;38(3):543-51.

19. Godefrooij M, Spigt M, van der Minne W, et al. Implementing cardiometabolic health checks in general practice: a qualitative process evaluation. *BMC Family Practice* 2014;15:132.

20. van Steenkiste B, van der Weijden T, Timmermans D, et al. Patients' ideas, fears and expectations of their coronary risk: barriers for primary prevention. *Patient Education & Counseling* 2004;55(2):301-7.

21. Nielsen KD, Dyhr L, Lauritzen T, et al. "Couldn't you have done just as well without the screening?". A qualitative study of benefits from screening as perceived by people without a high cardiovascular risk score. *Scandinavian Journal of Primary Health Care* 2009;27(2):111-6.

22. Sondergaard A, Christensen B, Maindal HT. Diversity and ambivalence in general practitioners' attitudes towards preventive health checks - a qualitative study. *BMC Family Practice* 2012;13:53.

23. Murphy M, McGloughlin M, Walkin S. The 'general check-up' in the asymptomatic adult-a study of GPs in the North West of Ireland. *European Journal of General Practice* 2015;21(1):58-62.

24. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ* 1991;303(6807):893-6. [published Online First: 1991/10/12]

25. [CG71] NCg. Familial hypercholesterolaemia: identification and management 2008.

26. Boregowda K, Rice S, Grey B, et al. Screening for familial hypercholesterolaemia. *Atherosclerosis* 2013;231 (2):e6-e7.

27. Bhatnagar D, Morgan J, Siddiq S, et al. Outcome of case finding among relatives of patients with known heterozygous familial hypercholesterolaemia. *BMJ* 2000;321(7275):1497-500.

28. Muir J, Neil A, Roe L, et al. Prevalence of risk factors for heart disease in OXCHECK trial: implications for screening in primary care. Imperial Cancer Research Fund OXCHECK Study Group. *BMJ* 1991;302(6784):1057-60.

29. Nherera L, Marks D, Minhas R, et al. Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. *Heart* 2011;97(14):1175-81.

30. Marks D, Wonderling D, Thorogood M, et al. Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis. *Health Technology Assessment (Winchester, England)* 2000;4(29):1-123.

31. Hozawa A, Folsom AR, Sharrett AR, et al. Does the impact of smoking on coronary heart disease differ by low-density lipoprotein cholesterol level?: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation Journal* 2006;70(9):1105-10.

32. Cheong KC, Yusoff AF, Ghazali SM, et al. Optimal BMI cut-off values for predicting diabetes, hypertension and hypercholesterolaemia in a multi-ethnic population. *Public Health Nutrition* 2013;16(3):453-9.

33. Park SH, Lee WY, Lee YS, et al. The relative effects of obesity and insulin resistance on cardiovascular risk factors in nondiabetic and normotensive men. *Korean Journal of Internal Medicine* 2004;19(2):75-80.

34. Thomas F, Bean K, Pannier B, et al. Cardiovascular mortality in overweight subjects: the key role of associated risk factors. *Hypertension* 2005;46(4):654-9.

35. Han TS, van Leer EM, Seidell JC, et al. Waist circumference as a screening tool for cardiovascular risk factors: evaluation of receiver operating characteristics (ROC). *Obesity Research* 1996;4(6):533-47.

36. Schunkert H, Moebus S, Hanisch J, et al. The correlation between waist circumference and ESC cardiovascular risk score: data from the German metabolic and cardiovascular risk project (GEMCAS). *Clinical Research in Cardiology* 2008;97(11):827-35.

37. Ashwell M, Gibson S. Waist to height ratio is a simple and effective obesity screening tool for cardiovascular risk factors: Analysis of data from the British National Diet And Nutrition Survey of adults aged 19-64 years. *Obesity Facts* 2009;2(2):97-103.

38. Lee KS, Park CY, Meng KH, et al. The association of cigarette smoking and alcohol consumption with other cardiovascular risk factors in men from Seoul, Korea. *Annals of Epidemiology* 1998;8(1):31-38.

39. Psota TL, Lohse B, West SG. Associations between eating competence and cardiovascular disease biomarkers. *Journal of Nutrition Education & Behavior* 2007;39(5 Suppl):S171-8.

40. Coghill N, Garside L, Montgomery A. NHS health checks: a cross- sectional observational study on equity of uptake and outcomes. *BMC Health Serv Res* 2018;18(1):238.

41. Crossan C, Lord J, Ryan R, et al. Cost effectiveness of case-finding strategies for primary prevention of cardiovascular disease: a modelling study. *British Journal of General Practice* 2017;67(654):e67-e77. . doi: 10.3399/bjgp16X687973. [published Online First: 2016 Nov 7]

42. Frich JC, Malterud K, Fugelli P. Women at risk of coronary heart disease experience barriers to diagnosis and treatment: a qualitative interview study. *Scandinavian Journal of Primary Health Care* 2006;24(1):38-43.

43. Chang KC, Soljak M, Lee JT, et al. Coverage of a national cardiovascular risk assessment and management programme (NHS Health Check): Retrospective database study. *Prev Med* 2015;78:1-8. doi: 10.1016/j.ypmed.2015.05.022 [published Online First: 2015 Jun 4]