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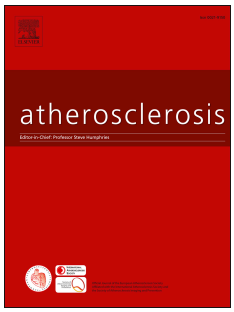

How does cholesterol burden change the case for investing in familial hypercholesterolaemia? A cost-effectiveness analysis

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Credit author statement

How does cholesterol burden change the case for investing in familial hypercholesterolaemia? A cost-effectiveness analysis

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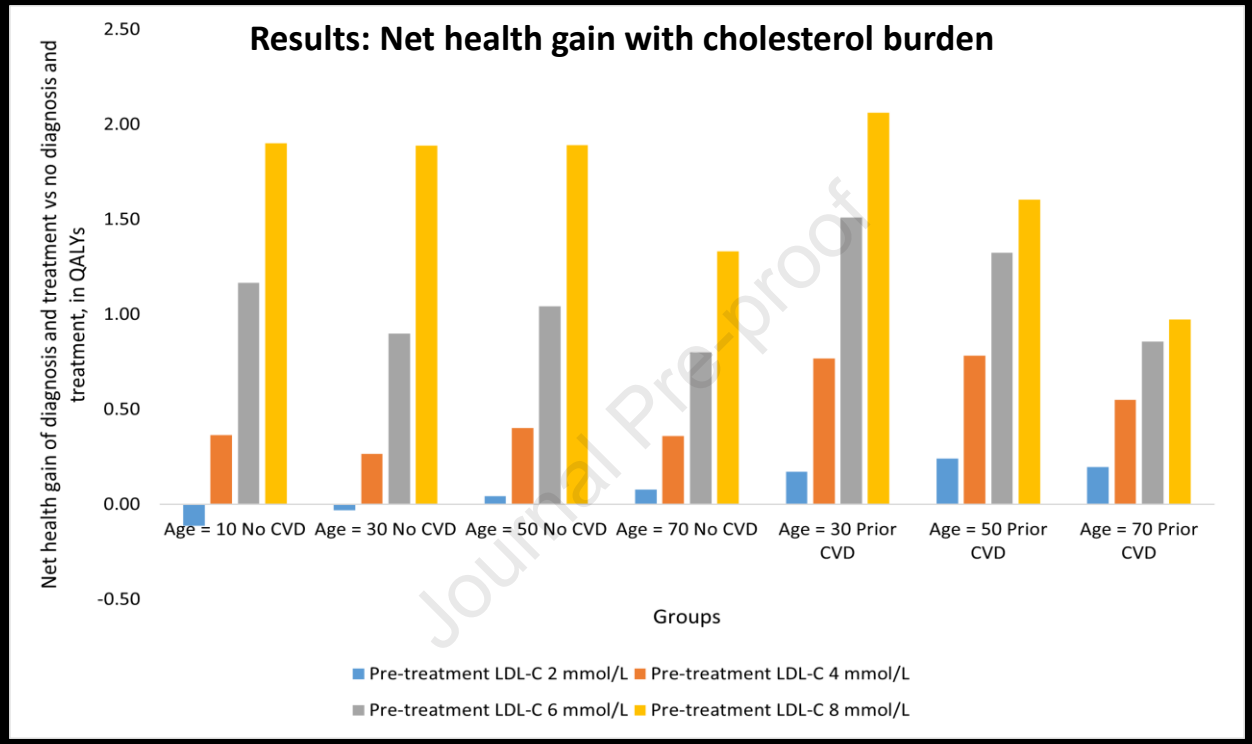
How does cholesterol burden change the case for investing in familial hypercholesterolaemia? A cost-effectiveness analysis

Objective

- To ascertain how the long-term benefits and costs of diagnosis and treatment of FH vary by prognostic factors and cholesterol burden.
- Cholesterol burden is the effect of long-term exposure to LDL-C on CVD risk.

Methods

- New cost-effectiveness model.
- Informed by UK NHS routine data of people with FH.
- Primary outcome = net health gain (in QALYs) given cost-effectiveness threshold of £15,000/QALY.
- Prognostic factors = pre-treatment LDL-C, age, gender, CVD history.



- With cholesterol burden, diagnosis resulted in positive net health gain) in all individuals with pre-treatment LDL-C ≥ 4 mmol/L, and in those with pre-treatment LDL-C ≥ 2 mmol/L aged ≥ 50 years or who have CVD history.
- If cholesterol burden is not considered, diagnosis resulted in lower net health gain, but still positive in children aged 10 years with pre-treatment LDL-C ≥ 6 mmol/L and adults aged 30 years with pre-treatment LDL-C ≥ 4 mmol/L.

Conclusions

- Diagnosis and treatment of most people with FH results in large net health gains, particularly in those with higher pre-treatment LDL-C.
- Considering cholesterol burden in cost-effectiveness modelling shows larger benefits from diagnosis and treatment.
- The magnitude of benefits also depends on prognostic factors, such as age, gender, LDL-C, and CVD history.
- Economic evaluations of FH interventions should consider the sensitivity of the study conclusions to cholesterol burden, particularly where interventions target younger patients
- Also consider prognostic factors such as pre-treatment LDL-C, age, and CVD history.

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Abbreviations: CVD: cardiovascular disease. FH: familial hypercholesterolaemia. LDL-C: Low-density lipoprotein cholesterol. NHS: National Health Service. QALY: quality-adjusted health year.

How does cholesterol burden change the case for investing in familial hypercholesterolaemia? A cost-effectiveness analysis

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Abstract

Background and aims:

This study aimed to ascertain how the long-term benefits and costs of diagnosis and treatment of familial hypercholesterolaemia (FH) vary by prognostic factors and 'cholesterol burden', which is the effect of long-term exposure to low-density lipoprotein cholesterol (LDL-C) on cardiovascular disease (CVD) risk.

Methods:

A new cost-effectiveness model was developed from the perspective of the UK National Health Service (NHS), informed by routine data from individuals with FH. The primary outcome was net health gain (i.e., health benefits net of the losses due to costs), expressed in quality-adjusted life years (QALYs) at the £15,000/QALY threshold. Prognostic factors included pre-treatment LDL-C, age, gender, and CVD history.

Results:

If cholesterol burden is considered, diagnosis resulted in positive net health gain (i.e., it is cost-effective) in all individuals with pre-treatment LDL-C ≥ 4 mmol/L, and in those with pre-treatment LDL-C ≥ 2 mmol/L aged ≥ 50 years or who have CVD history. If cholesterol burden is not considered, diagnosis resulted in lower net health gain, but still positive in children aged 10 years with pre-treatment LDL-C ≥ 6 mmol/L and adults aged 30 years with pre-treatment LDL-C ≥ 4 mmol/L.

Conclusions:

Diagnosis and treatment of most people with FH results in large net health gains, particularly in those with higher pre-treatment LDL-C. Economic evaluations of FH interventions should consider the sensitivity of the study conclusions to cholesterol burden, particularly where interventions target younger patients, and explicitly consider prognostic factors such as pre-treatment LDL-C, age, and CVD history.

Keywords

Familial hypercholesterolaemia, cost-effectiveness, cholesterol

1. Introduction

There is widespread consensus that early diagnosis and treatment of familial hypercholesterolaemia (FH) are effective, safe, cost-effective, and inexpensive [1–9]. Nonetheless little is known about the magnitude of health losses and costs due to underdiagnosis and the benefits from diagnosis and treatment, and how it varies depending on prognostic factors, such as pre-treatment low density lipoprotein cholesterol (LDL-C) levels. Furthermore, in individuals with FH, the duration of exposure to high LDL-C is an important determinant of cardiovascular disease risk (CVD) – termed "cholesterol burden" [10,11]. However, cost-effectiveness studies have not examined the impact of cholesterol burden on their results [4–9]. This evidence is needed to inform decisions about how much a healthcare service should invest in FH, and which policies should be implemented to improve diagnosis (e.g., cascade testing, population-level screening) and treatment (e.g., cholesterol lowering using different agents, treatment intensity).

To address this gap, this study estimated the health benefits and costs of diagnosis and treatment of people with FH over their expected lifetime (compared to no diagnosis and no treatment), considering key prognostic factors, and under two alternative scenarios, with and without considering cholesterol burden. This study uses a cost-effectiveness model informed by real-world routinely collected data from a cohort of people with FH in England.

2. Materials and methods

The cost-effectiveness analysis took the perspective of the UK National Health Service (NHS) at a 2019 price base, and discounting future costs and health benefits to their present value at 3.5% per annum [12] .

The cost-effectiveness model simulated the outcomes of hypothetical groups of people with FH, termed "subpopulations", if they had been diagnosed and treated, and if they had not been diagnosed and remained untreated until their first CVD event. The subpopulations were defined according to the key prognostic factors of age at diagnosis (10, 30, 50, and 70 years), sex, prior

cardiovascular history, and pre-treatment LDL-C (2, 4, 6, and 8 mmol/L), selected given their impact on CVD risk [1–3].

The primary outcome was the net health gain from diagnosing and treating individuals with FH compared to no diagnosis (and no treatment), expressed in quality-adjusted life years (QALYs) and discounted to present values [13]. A positive net health gain means that diagnosis (and treatment) is cost-effective, with larger gains translating into larger scope for investment. Net health gain is equivalent to the calculation of the incremental cost-effectiveness ratio. If the net health gain is positive, the incremental cost-effectiveness ratio is necessarily below the cost-effectiveness threshold. To convert additional NHS costs to health losses, the cost-effectiveness thresholds of £15,000/QALY (primary analysis) and £20,000/QALY (secondary analysis) were used. The £15,000/QALY threshold is used in impact assessments by the UK Department of Health and Social Care [14,15], while £20,000/QALY is the lower bound of the threshold used by the UK National Institute for Health and Care Excellence (NICE) in deciding whether new drugs should be reimbursed by the NHS [12].

The secondary outcomes were undiscounted gains in event-free life expectancy (in years), life expectancy (in years), quality-adjusted life expectancy (in QALYs), and impact on undiscounted NHS costs (in pound sterling).

2.1 Model structure

Figure 1 shows the model structure. It is a cohort Markov model with annual cycles and half-cycle correction, built in MS Office Excel® 2016. The model structure was informed by previous cost-effectiveness models in FH and CVD [4–9,16], and clinical feedback. In the base-case, diagnosis and management were assumed to reduce CVD risk in those aged ≥ 25 years and to reduce all-cause mortality.

2.2 Model inputs

2.2.1 Effect of diagnosis on LDL-C and CVD risk

All model inputs are presented in the *Supplementary Material List of model inputs*. Table 1 shows the model inputs related to the effect of diagnosis (and treatment) on LDL-C and CVD risk.

The effect of diagnosis (and treatment) on LDL-C was estimated from a cohort of individuals recorded in England's Clinical Practice Research Datalink (CPRD) aged ≥ 18 years with a recorded diagnosis of FH between 01/01/1999-22/07/2016, who had an eligible linkage to Hospital Episode Statistics, who had received their FH diagnosis after their practice met CPRD minimum data quality criteria and who were treated before or within 2 years of the FH diagnosis - henceforth termed the 'CPRD-FH cohort'. The CPRD-FH cohort comprised 2,135 individuals with routinely collected primary care data linked to hospital care (via Hospital Episode Statistics) and mortality data (via the Office of National Statistics) (see *Supplementary Table 1* for their characteristics). LDL-C response to treatment was estimated as the percentage reduction in LDL-C as recorded in an individual's primary care records before and 2 years after cholesterol-lowering treatment see (*Supplementary Appendix, Estimation of LDL-C response to cholesterol lowering treatment for details*). Access to the data and ethical approval was granted by the CPRD Independent Scientific Advisory Committee (Protocol number 18_143).

Cholesterol burden was considered using the equation proposed by the 2017 European Consensus Statement [11] relating 1 mmol/L reduction in LDL-C over a period of time to the reduction in cardiovascular risk, assuming that the number of years of treatment corresponded to the number of years since diagnosis. Under the cholesterol burden scenario, the effect of diagnosis and treatment on cardiovascular risk increases as people age. For example, for a 1 mmol/L reduction in LDL-C, 10 years' treatment leads to a 28% reduction in CVD risk whereas 20 years' treatment leads to 38%.

The alternative scenario, without cholesterol burden, assumed that the change in cardiovascular event risk was unaffected by the duration of treatment and corresponded to the

reduction in major vascular event risk estimated by a large meta-analysis of statin trials at 21% per 1 mmol/L reduction in LDL-C [17].

2.2.2 Risk of CVD events and death

Major CVD event risk in individuals diagnosed and treated was estimated from the CPRD-FH cohort data. A major CVD event was defined as any new clinical diagnosis of coronary heart disease (including acute coronary syndrome (ACS), unstable angina, unspecified ACS, and myocardial infarction), transient ischaemic attack (TIA), ischaemic stroke (IS), and CVD death (including death due to CVD causes and any death within 28 days of a CVD event) according to the individuals' primary care, secondary care, and mortality records.

Parametric survival analysis was used to project CVD risk beyond the CPRD-FH cohort follow-up in individuals who are diagnosed and treated. The generalised gamma distribution was selected for the base-case, and the exponential distribution for a scenario, given that they had the best visual and statistical fit [18]. Both the generalised gamma and the exponential distributions predicted an approximately constant CVD risk beyond the follow-up period. Therefore, a US study of individuals with the FH phenotype with follow-up of 30-years [19] was used to adjust the predicted risk upwards from 10 years post-diagnosis. For details, see *Supplementary Appendix, Analysis of the risk of first major CVD event.*

The risk in undiagnosed (and untreated) individuals is not observable because undiagnosed individuals are only identified after diagnosis. The risk if the hypothetical cohort had not been diagnosed (and not treated) was estimated from the risk estimated from the CPRD-FH cohort, who were all treated, by 'removing' the beneficial effects of diagnosis and treatment. This involved (1) estimating the absolute reduction in absolute LDL-C achieved; (2) calculating the risk reduction that corresponds to this LDL-C reduction (with and without considering cholesterol burden, depending on the scenario); (3) applying the reciprocal of this risk reduction to the CVD risk estimated from the parametric survival analysis for individuals who were diagnosed and treated.

The risk of death following a non-fatal CVD event was based on published risk equations from a large Scottish study (N=3,184 people who had a first non-fatal event) with long follow-up (median follow-up 4.8-7.6 years depending on sex and CVD event group) [20], because the number of death events in the CPRD-FH cohort was insufficient to allow for their robust estimation. For details, see *Supplementary Appendix, Mortality following non-fatal CVD events*.

2.2.3 Costs and health-related quality of life

The impact of diagnosis on costs includes the cost of cholesterol-lowering medication, monitoring, and management of adverse events from treatment. The cost of cholesterol-lowering medication was based on the drugs prescribed to the CPRD-FH cohort, at £21 per annum. The cost of monitoring was based on the nature and frequency of healthcare appointments and tests advised by the NICE guideline and clinical feedback [22,23] and is presented in Table 2. The cost of the management of adverse effects was based on the NICE clinical guideline on lipid lowering treatment (which informed the NICE guideline on familial hypercholesterolaemia) at £3 for primary prevention and £6 for secondary prevention (both per annum) [16,22].

The costs of CVD events were based on a study of the healthcare costs of individuals with stable coronary artery disease in England (N=94,966, between 2001-2010) [24].

The health-related quality of life weights related to CVD events were obtained from the NICE clinical guideline [16], adjusted for age and sex [25].

Analysis

The base-case results are probabilistic, being calculated as the mean over 5,000 Monte Carlo simulations [29]. Model validation is reported in *Supplementary Appendix, Validation*. The sensitivity analysis tested 30 alternative assumptions and model inputs, run deterministically given the similarity between probabilistic and deterministic results (*Supplementary Appendix, Scenario Analysis* for details).

3. Results

Results for all subgroups, in terms of the mean and standard deviation, are presented in *Supplementary Tables 33 and 35*.

3.1 Primary outcome: net health benefit

If cholesterol burden is considered, the net health gain from diagnosis (and treatment) at the cost-effectiveness threshold of £15,000/QALY ranges from -0.11 to 2.06 QALYs per individual across the subpopulations (Figure 3A). Net health gain is positive (hence diagnosis is cost-effective for the NHS) in all subpopulations with pre-treatment LDL-C ≥ 4 mmol/L, and in those with pre-treatment LDL-C ≥ 2 mmol/L aged ≥ 50 years or who have CVD history. Net health gains for a cost-effectiveness threshold of £20,000/QALY follow a similar pattern (*Supplementary Figure 13*), with the major difference being that gains are positive for all subpopulations except those aged 10 years with pre-treatment LDL-C ≤ 2 mmol/L. Net health gain depends on the prognostic factors. All else being equal, gains are larger if subpopulations have higher pre-treatment LDL-C levels.

If cholesterol burden is not considered, net health gains are lower at -0.23 to 1.59 QALYs per individual across the subpopulations (Figure 2B). As with the analysis considering cholesterol burden, diagnosis results in positive net health gains in most subpopulations. However, there are more subpopulations for whom diagnosis is a negative net health gain; i.e., it is not cost-effective. These are children aged 10 years with pre-treatment LDL-C ≤ 4 mmol/L and adults aged 30 years with pre-treatment LDL-C ≤ 2 mmol/L. Net health gains increase with greater LDL-C levels and for older ages at diagnosis, which reflects the greater CVD risk in individuals at older ages.

The impact of cholesterol burden on net health gain depends on age. For example, the net health gain in subpopulations aged 10 years with pre-treatment LDL-C = 8 mmol/L is 0.49 QALYs per individual without considering cholesterol burden *vs* 1.90 QALYs considering cholesterol burden (approximately 3.8 times larger). In subpopulations aged 50 years with pre-treatment LDL-C = 8 mmol/L, the gain is 1.36 QALYs per individual without considering cholesterol burden vs 1.89 QALYs considering cholesterol burden (39% larger). The difference is more pronounced for younger

subpopulations due to their longer exposure period, hence they have longer to benefit from treatment, which results in lower LDL-C exposure.

Net health gains can be converted into monetary units (to net monetary gains) to understand the magnitude of the investment warranted in diagnosis. As with the net health gains, the investment warranted in diagnosis and treatment varies by subpopulations' prognostic factors and depends on whether cholesterol burden is considered. For example, at the cost-effectiveness threshold of £15,000/QALY, if considering cholesterol burden, the investment warranted can be as little as £663 per individual for subpopulations aged 50 years and pre-treatment LDL-C = 2 mmol/L, but approximately £28,000 if pre-treatment LDL-C = 8 mmol/L. If cholesterol burden is not considered, it is £15 per individual for subpopulations aged 50 years and pre-treatment LDL-C = 2 mmol/L and approximately £20,000 if pre-treatment LDL-C = 8 mmol/L (*Supplementary Table 37*).

3.2 Secondary outcomes

If cholesterol burden is considered, event-free life expectancy gain from diagnosis and treatment ranged between 0.5-25 years per individual across the subpopulations (Figure 4A). Event-free life expectancy gain is greater if diagnosis occurs at a younger age, in subpopulations with higher pre-treatment LDL-C, and in subpopulations with CVD history. Life expectancy and quality adjusted-life expectancy gains follow a similar pattern as the event-free life expectancy gains (*Supplementary Figures 16-17*). Diagnosis and treatment results in cost savings to the NHS in subpopulations with pre-treatment LDL-C $\geq$ 4 mmol/L if aged 10 years or with CVD history, or pre-treatment LDL-C $\geq$ 6 mmol/L if aged 30 years and older and without CVD history (*Supplementary Figures 18*).

If cholesterol burden is not considered, event-free life expectancy gain is lower at 0.4-11 years per individual across the subpopulations, albeit the pattern is similar to the analysis with cholesterol burden (see Figure 4B). Life expectancy and quality-adjusted life expectancy gains are also lower at up to 4 years and 4 QALYs per individual respectively (*Supplementary Figures 19-20*). Diagnosis and treatment results in cost savings to the NHS in subpopulations who have pre-treatment

LDL-C ≥ 8 mmol/L, if pre-treatment LDL-C ≥ 6 mmol/L if aged ≥ 50 years of age, and if pre-treatment LDL-C ≥ 4 mmol/L if with CVD history (*Supplementary Figure 21*).

3.3 Uncertainty and scenario analysis

Uncertainty related to the assumptions related to the model design and parameterisation were assessed with scenario analysis. The results were robust to most scenarios (*Supplementary Tables 38-39*). Irrespective of whether cholesterol burden is considered, the scenario with the greatest impact on the number of subpopulations for whom diagnosis is a positive net health gain is the scenario assuming that those with LDL-C ≤2 mmol/L are not actively treated with cholesterol-lowering therapy and have no benefits from diagnosis (nine fewer subpopulations if considering cholesterol burden and eight fewer without cholesterol burden). Scenarios with net health gain from diagnosis was positive in more subpopulations were those where diagnosis and treatment reduced LDL-C to a greater extent than the 33% reduction in the base-case, such as the scenario where diagnosis reduced LDL-C by 50% as per NICE target [2] (compared to 33% reduction in the base-case); and scenarios where the long-term CVD risk was higher than in the base-case (e.g., using the exponential parametric model rather than the generalised gamma model in base-case); and the scenario assuming that monitoring following diagnosis involved fewer medical appointments compared to the base-case. If achieving the NICE recommended target of 50% reduction in LDL-C requires a large increase in treatment costs, gains from diagnosis and treatment are lower (see Online Supplementary Material Figures 26-27 for illustrative scenarios). Probabilistic sensitivity analysis results suggest that parameter uncertainty has a small impact on the decision uncertainty (see *Supplementary Figures 22-25)*.

4. Discussion

This study is the first to estimate the net health gain of diagnosing and treating individuals with FH, depending on prognostic factors, and with and without considering the impact of including cholesterol burden. CVD risk and LDL-C response to treatment were estimated from routinely

collected data of individuals with FH in England, which subsequently informed a new cost-effectiveness model. The cost-effectiveness model included key prognostic factors, namely pre-treatment LDL-C, age at diagnosis, gender, and CVD history, which allowed for the estimation of subpopulation-specific long-term health outcomes, costs, and net health gain. These results can inform the design of policies for diagnosis that target individuals with different characteristics (e.g., cascade screening versus universal screening with LDL-C in childhood). Furthermore, the cost-effectiveness model can be easily adapted to evaluate new drugs and treatment policies which may increase LDL-C reductions but have greater costs, as well as to use inputs from other countries (e.g., unit costs, management practices) to provide country-specific results.

Diagnosis and treatment of individuals with FH generally leads to large net health gains for the NHS. That is, given the health benefits to people with FH and the impact on NHS costs, it is cost-effective to diagnose and treat most individuals with FH over specific LDL-C levels (individuals with pre-treatment LDL-C $\geq$ 4 mmol/L and those with LDL-C $\geq$2 mmol/L and aged $\geq$ 50 years of age; or with CVD history). This means that there is scope for investment in better diagnosis and potentially more intensive (and effective) treatment strategies). The large magnitude of net health gains suggests that investment in infrastructure for more diagnosis and treatment are likely to be good value for money to the NHS.

Cholesterol burden is a major driver of cost-effectiveness results, whilst its magnitude being a key uncertainty. In the cost-effectiveness model, cholesterol burden was explicitly incorporated using the European Atherosclerosis Society Consensus Statement equation [11]. This equation was based on reviews of studies mostly from individuals without FH, hence its generalisability to individuals with FH is uncertain. When cholesterol burden was not considered, the effect of LDL-C on cardiovascular risk was constant over time and based on a large meta-analysis of statin trials [17]. However, the trials had a relatively short follow-up, while cholesterol burden effects may be clearer over a long follow-up. If cholesterol burden is underestimated or not included, more costly and more effective diagnostic and treatment policies may, incorrectly, not be recommended. This will affect mostly younger individuals with FH, given the results of this study that, if cholesterol burden was not considered, the

difference in the magnitude of net health gains was larger in younger subpopulations. For these reasons, further research is required to quantify the long-term effect of reductions in LDL-C on cardiovascular risk in individuals with FH and methods to incorporate those effects in cost-effectiveness modelling.

Pre-treatment LDL-C has the largest influence on net health gains, of those prognostic factors explored in this study. This influence occurs via two mechanisms: as a prognostic factor, given that LDL-C increases CVD risk; and because, for the same proportional reduction in LDL-C, higher LDL-C levels result in greater absolute reductions, which in turn determine the reduction on cardiovascular risk from treatment. Net health gains also depended on age and CVD history. The implication for future investment appraisals and cost-effectiveness analyses of diagnostic and management policies is that prognostic factors, importantly pre-treatment LDL-C but also age and prior cardiovascular history, should be explicitly accounted for.

4.1 Comparison with other studies

Although the impact of diagnosis and treatment of people with FH has not been examined in the literature, previous cost-effectiveness analyses of cascade screening found that screening is cost-effective [4,6–9]. Hence it can be inferred that diagnosis and treatment represents a net health gain, in line with the results presented here. The magnitude of net health gain is difficult to compare to these other studies due to the lack of population stratification by prognostic factors. For example, given the results presented in Crosland et al [6], the net health gain from diagnosis in adults aged ≥ 40 years can be calculated at 0.94 QALYs at the £15,000/QALY threshold. In the present study, the net health gain in individuals aged 50 years ranged between 0.08-1.83 QALYs depending on pre-treatment LDL-C levels if cholesterol burden is included and 0-1.36 QALYs if not, hence the Crosland et al estimates are broadly in the midpoint of the present estimates.

4.2 Limitations

The limitations stem mostly from the limitations of the data used to inform the cost-effectiveness model. Although the CPRD-FH was reasonably large (N=2,135), the number of events

precluded the estimation of risk of recurrent events. Therefore, the estimation of risk of death following a non-fatal cardiovascular event, which was based on a study in individuals mostly without FH [20]. Furthermore, younger individuals and individuals with lower pre-treatment LDL-C were under-represented in the CPRD-FH cohort, increasing the uncertainty around the model results for younger groups and those with pre-treatment LDL-C = 2 mmol/L. It was not feasible to differentiate between homozygous and heterozygous FH, hence these results may not generalise to people with homozygous FH. Due to the sparse data beyond 10 years, the extrapolation of long-term cardiovascular risk had limited face validity, hence the adjustment using an external study in individuals with the FH phenotype [19]. Additionally, there is some uncertainty about the extent to which the coding of individuals in primary care is accurate and complete, hence the generalisability of the CPRD-FH cohort to individuals with FH. This analysis compared diagnosis and treatment to the absence of diagnosis and no treatment, however some individuals may be treated, albeit suboptimally, in the absence of diagnosis. Other uncertainties relate to the effect of diagnosis and treatment on LDL-C and on costs of monitoring post-diagnosis, given the variability in management practices across the country and over time, and individual LDL-C response. It was outside the scope of this study to investigate the relationship between the effectiveness of treatment in reducing LDL-C and its intensity (hence its costs).

4.3 Conclusion

Diagnosis and treatment of individuals with FH results in large net health gains, hence large scope for investment in diagnosis by the NHS, not only to support diagnosis and treatment but also in infrastructure and organisation. The magnitude of gains depends on prognostic factors, particularly pre-treatment LDL-C, age at diagnosis, and cardiovascular history. Most importantly, on whether the increased effect of exposure to raised LDL-C levels on cardiovascular risk, termed cholesterol burden, is considered. Given their impact on net health gain, future evaluations of policies for the diagnosis and treatment of individuals with FH should explicitly consider the effect of these prognostic factors and of cholesterol burden. Further research should explore approaches to quantify cholesterol burden in individuals with FH.

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Declaration of interests

Rita Faria declares that, since the research was completed, she has become an employee of Astellas Pharma Europe Ltd.

Stephen Weng was part of an institution that received grants from the NIHR SPCR for research related to Familial Hypercholesterolaemia, consulting fees from his Academic Advisory Committee for Road to Health Ltd, Honoraria and travel fees from Amgen for lectures on familial hypercholesterolaemia, was previously a committee member for the MHRA CPRD Independent Scientific Advisory Committee and is currently employed by Janssen R&D.

Steve Humphries has received Support from the British Heart Foundation (PG 008/08) and is the director of the UK Paediatric FH Register which has received support from a grant from the International Atherosclerosis Society (Pfizer number 24052829) and a medical director and minor share holder of a UCL Spin-out company StoreGene which offers DNA testing for individuals with FH.

Nadeem Qureshi has received grants from NIHR SPCR and MRC (NUOF), Honoraria from Amgen for lectures on familial hypercholesterolaemia, is a Member of the Board for the NIHR School for Primary Care Research (2021-) and a Member of Medical, Scientific & Research Committee of HeartUK.

Edward Cox, Pedro Saramago Goncalves, Ralph Akyea, Barbara Iyen and Beth Woods have no conflicts of interest to declare.

Author contributions

Rita Faria developed the cost-effectiveness model, conducted the analysis, contributed to the individual participant level analysis of the CPRD-FH cohort, and wrote the first and subsequent drafts of the manuscript and supplementary material.

Pedro Saramago Goncalves conducted the individual participant level analysis of the CPRD-FH cohort, wrote sections of the supplementary material, collaborated in cost-effectiveness model development, analysis, and to reviewing and editing the manuscript.

Edward Cox collaborated in the CPRD-FH data analysis, cost-effectiveness model development, analysis, and to reviewing and editing the manuscript.

Stephen Weng contributed to the development of the funding application, led the acquisition and the preparation of the CPRD-FH data, contributed to the CPRD-FH data analysis, cost-effectiveness model development, analysis, and to reviewing and editing the manuscript.

Barbara Iyen contributed to the preparation of the CPRD-FH data, its analysis, cost-effectiveness model development, analysis, and to reviewing and editing the manuscript.

Ralph K. Akyea contributed to the preparation of the CPRD-FH data, its analysis, cost-effectiveness model development, analysis, and to reviewing and editing the manuscript.

Steve E Humphries contributed to the development of the funding application, CPRD-FH data analysis, cost-effectiveness model development, analysis, and to reviewing and editing the manuscript.

Nadeem Qureshi led the development of the funding application and management of the overall study (HTA – 15/134/02), and contributed to the CPRD-FH data analysis, cost-effectiveness model development, analysis, and to reviewing and editing the manuscript.

Beth Woods contributed to the development of the funding application, led the health economics workstream (CPRD-FH data analysis, cost-effectiveness model development and analysis), and contributed to reviewing and editing the manuscript.

All authors approved the final manuscript.

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The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health & Social Care.

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Tables

Table 1: Model inputs related to the effect of diagnosis and treatment on cardiovascular risk

Parameter	**Value**	**Source**
Reduction in LDL-C due to FH diagnosis	33.4%	Analysis of CPRD-FH cohort
Effect of reducing LDL-C by 1 mmol/L on the risk of CVD events if cholesterol burden is considered.	Calculated according to EAS equation [a]	EAS Consensus Statement [33]
Effect of reducing LDL-C by 1 mmol/L on the risk of CVD events if cholesterol burden not considered.	0.79	Published meta-analysis of randomised controlled trials of statins [17]
Effect of reducing LDL-C by 1 mmol/L on the risk of non-vascular death	0.96	

[a] The European Atherosclerosis Society Consensus Statement equation is $(exp^{(-0.249+(number\ of\ years\ of\ treatment-5)\times(-0.0152)})$ [11].

CVD: cardiovascular disease. CPRD-FH cohort: cohort of individuals with recorded diagnosis of FH as described in the text. EAS: European Atherosclerosis Society. FH: familial hypercholesterolaemia. LDL-C: low-density lipoprotein cholesterol.

Table 2: Monitoring pattern and costs following diagnosis

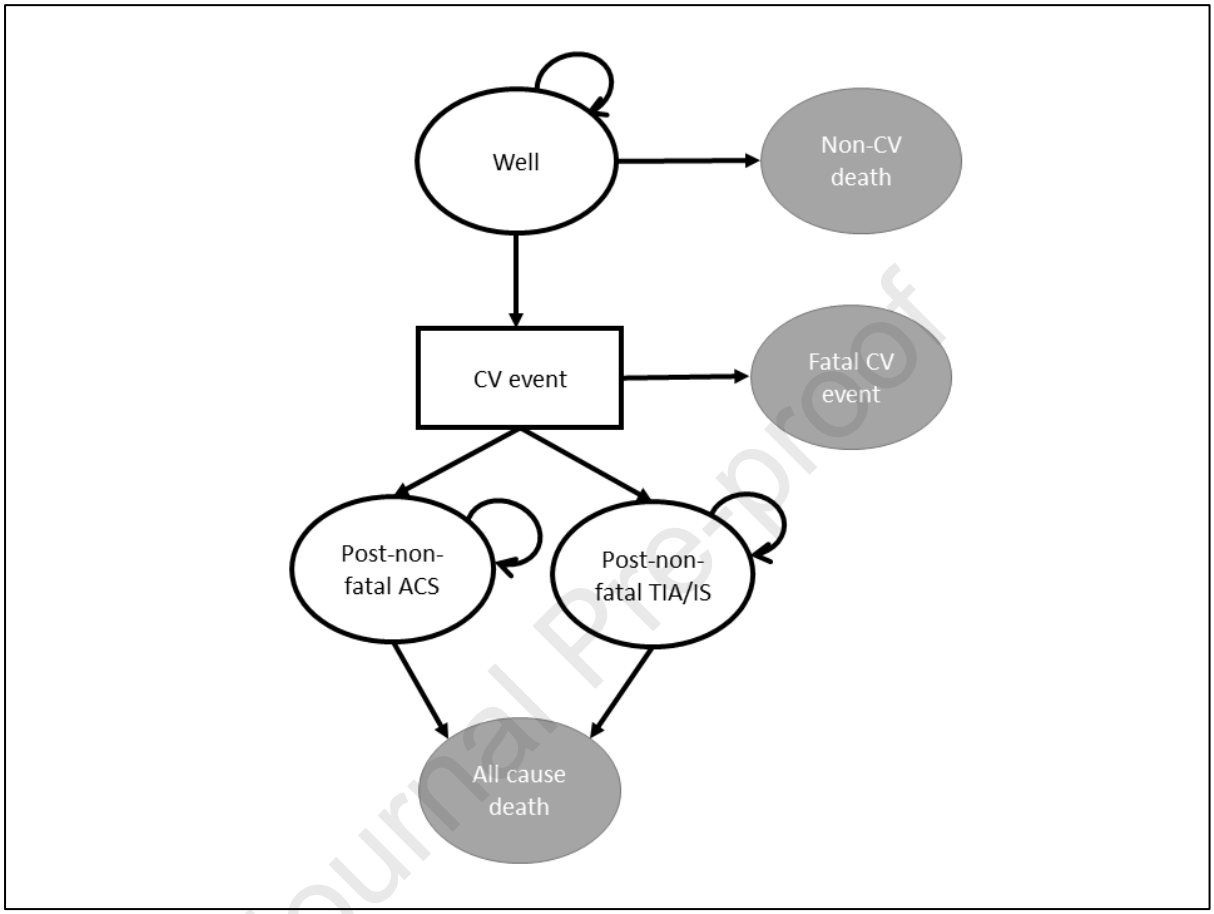
Monitoring and treatment	Number of appointments per year	Mean cost per year
Adults		
Primary care Year 1: number of appointments (& lipid tests)	3.0	£137
Primary care Year 2+: number of appointments (& lipid tests)	1.0	£35
Secondary care Year 1: number of appointments (& lipid tests)	3.0	£556
Secondary care Year 2+: number of appointments (& lipid tests)	1.0	£170
Children and adolescents		
Year 1: number of appointments (& lipid tests)	3.0	£723
Year 2+: number of appointments (& lipid tests)	1.5	£336

The base-case assumes that 25% of adult patients are monitored in secondary care, with the remaining being monitored in primary care [26].

Unit costs were obtained from national sources and inflated to 2019 prices as required [27,28].

Figures

Figure 1: Model diagram

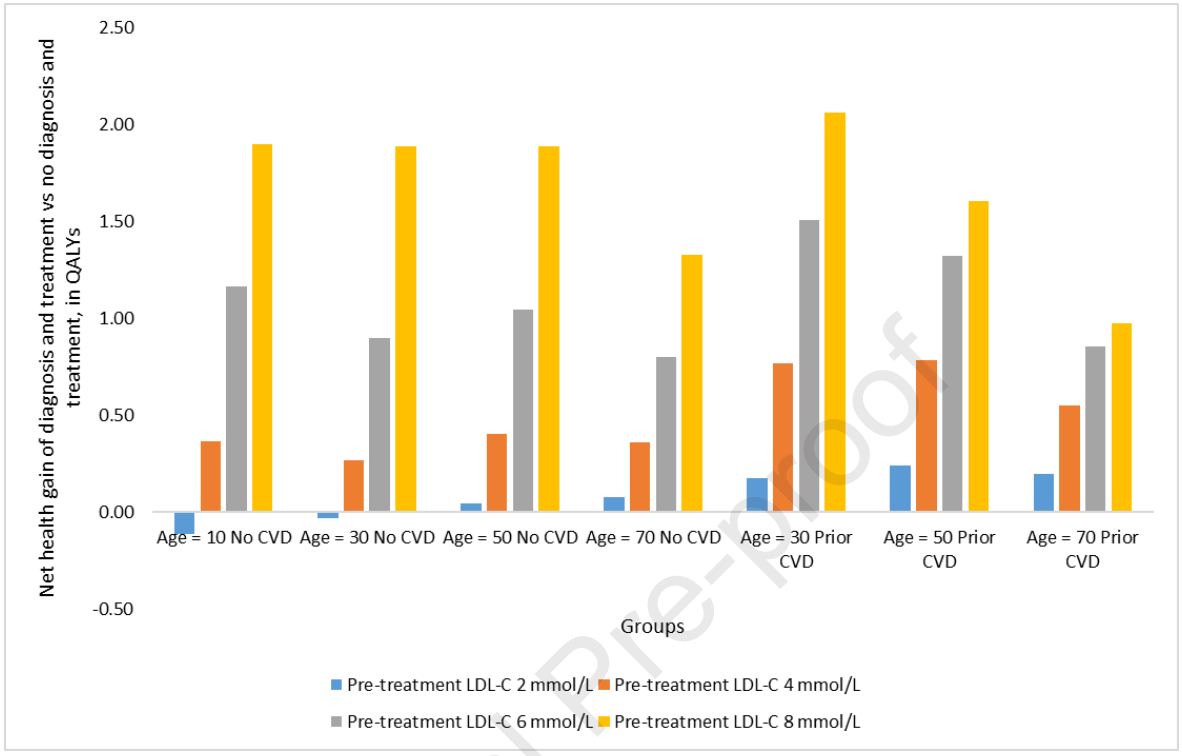


Individuals enter the model in the 'well state' at the time of diagnosis and are at risk of a first major cardiovascular event and non- cardiovascular death. Following a non-fatal event, individuals are at risk of all-cause death.

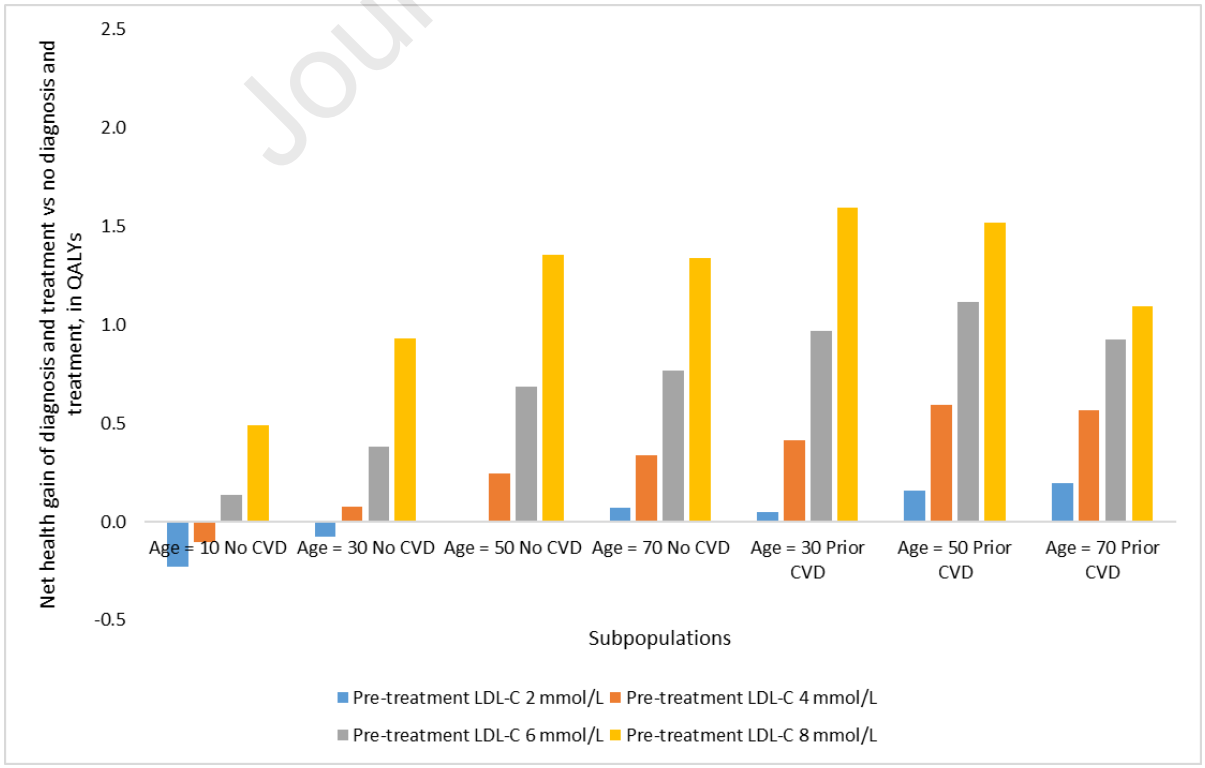
ACS: acute coronary syndrome. CVD: cardiovascular. IS: ischaemic stroke. TIA: transient ischaemic attack.

Figure 2: Net health gain from diagnosis and treatment

(A)



(B)

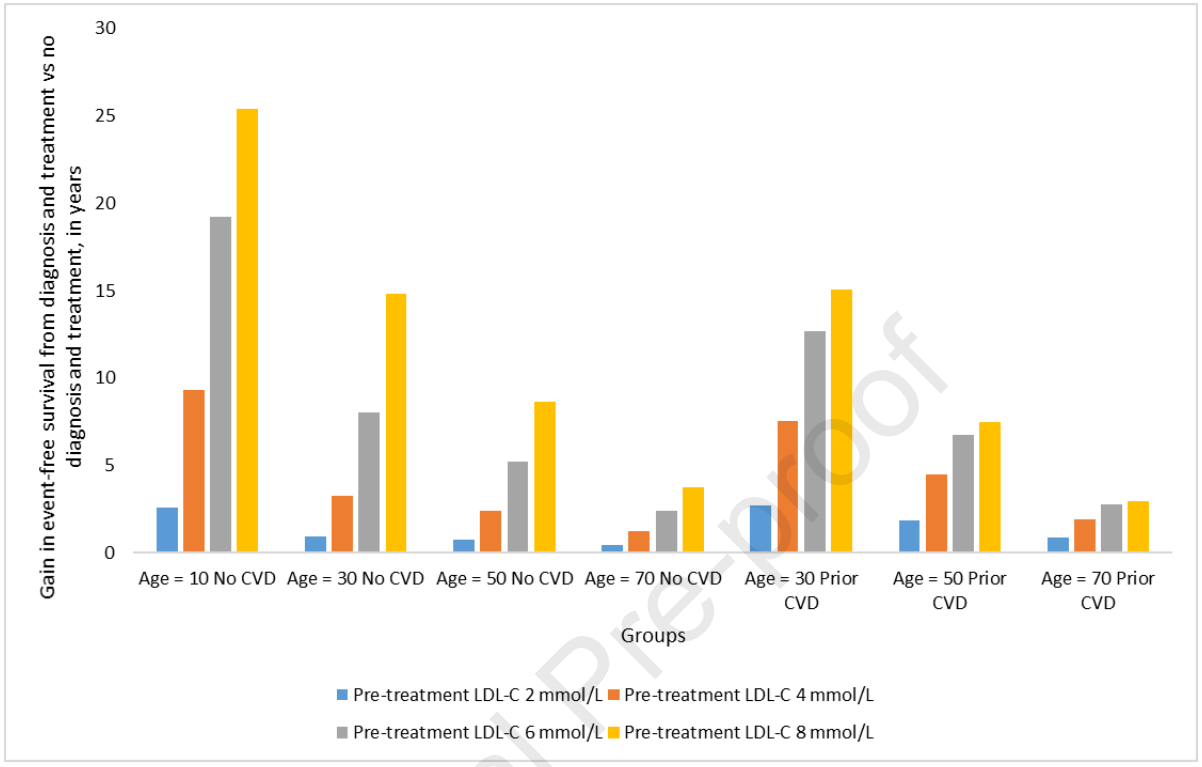


Positive gains in net health benefit, that is, bars over the zero line, indicate that diagnosis (and treatment) is cost-effective at the cost-effectiveness threshold of £15,000/QALY. Numerical estimates presented in *Supplementary Table 34* (considering cholesterol burden) and *Table 36* (not considering cholesterol burden).

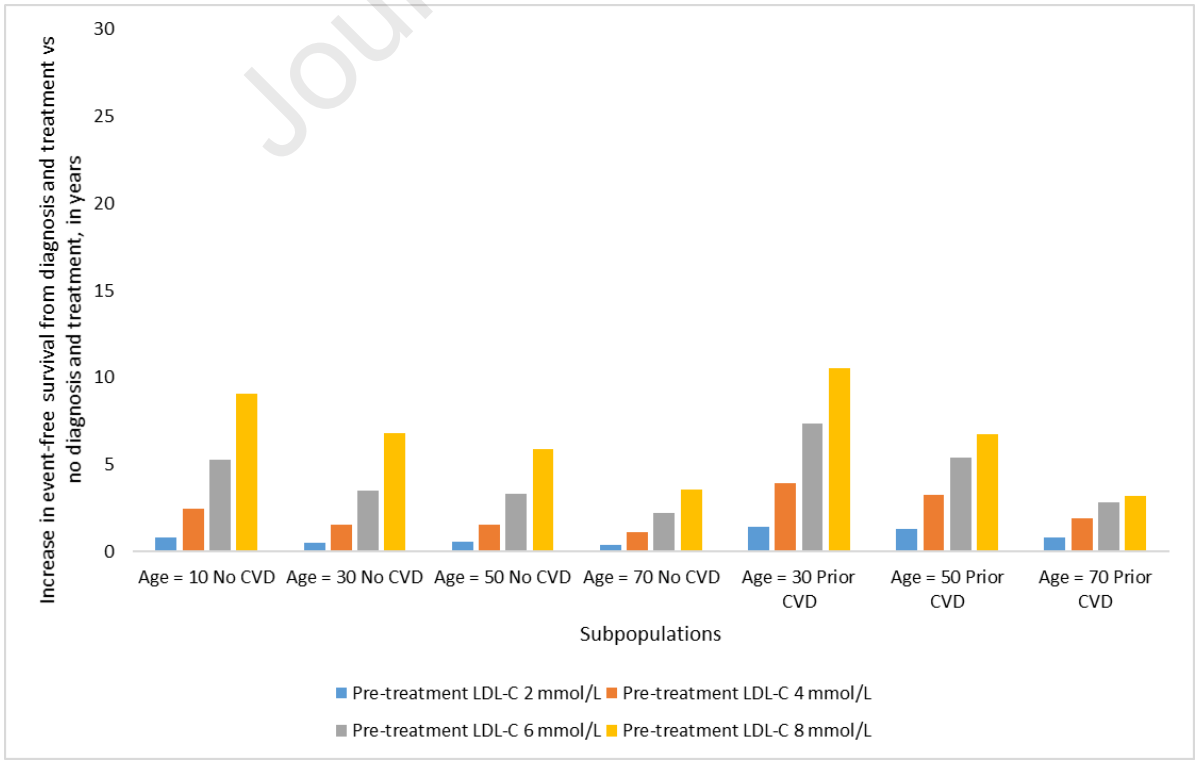
(A) Considering cholesterol burden. (B) Not considering cholesterol burden. CVD: Cardiovascular disease. LDL-C: low density lipoprotein cholesterol. QALY: quality-adjusted life year. QALYs: Quality-adjusted life years.

Figure 3: Gains in event-free life expectancy from diagnosis and treatment

(A)

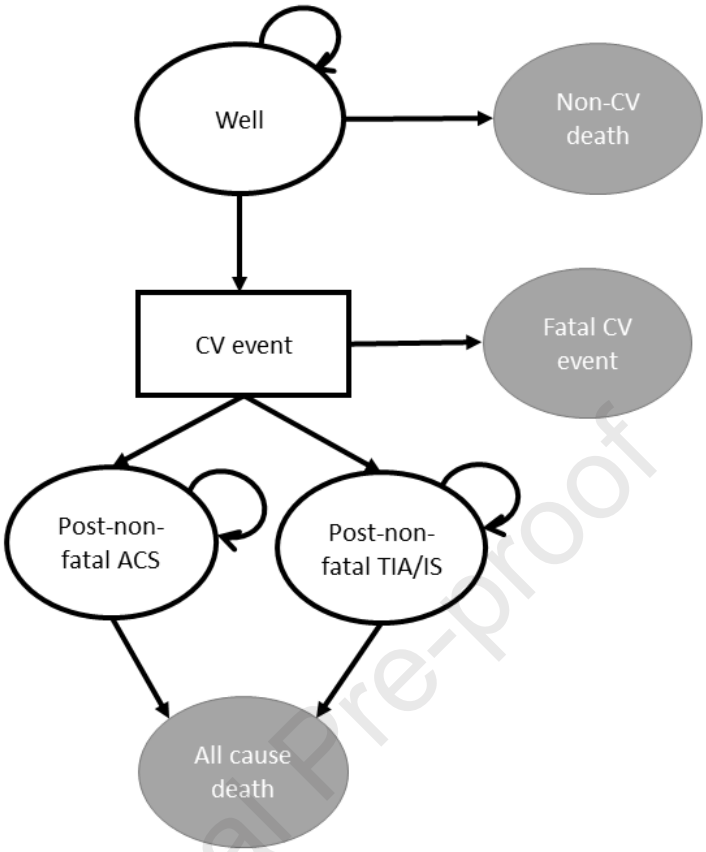


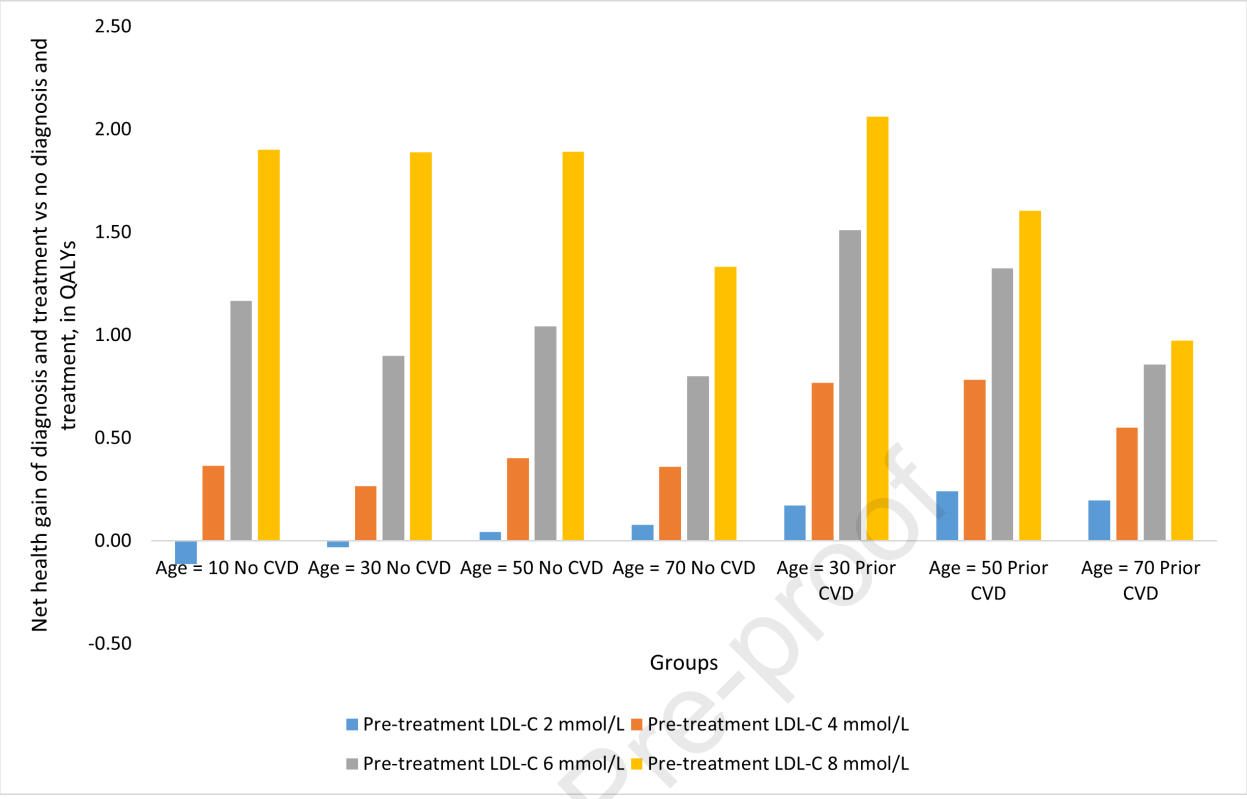
(B)

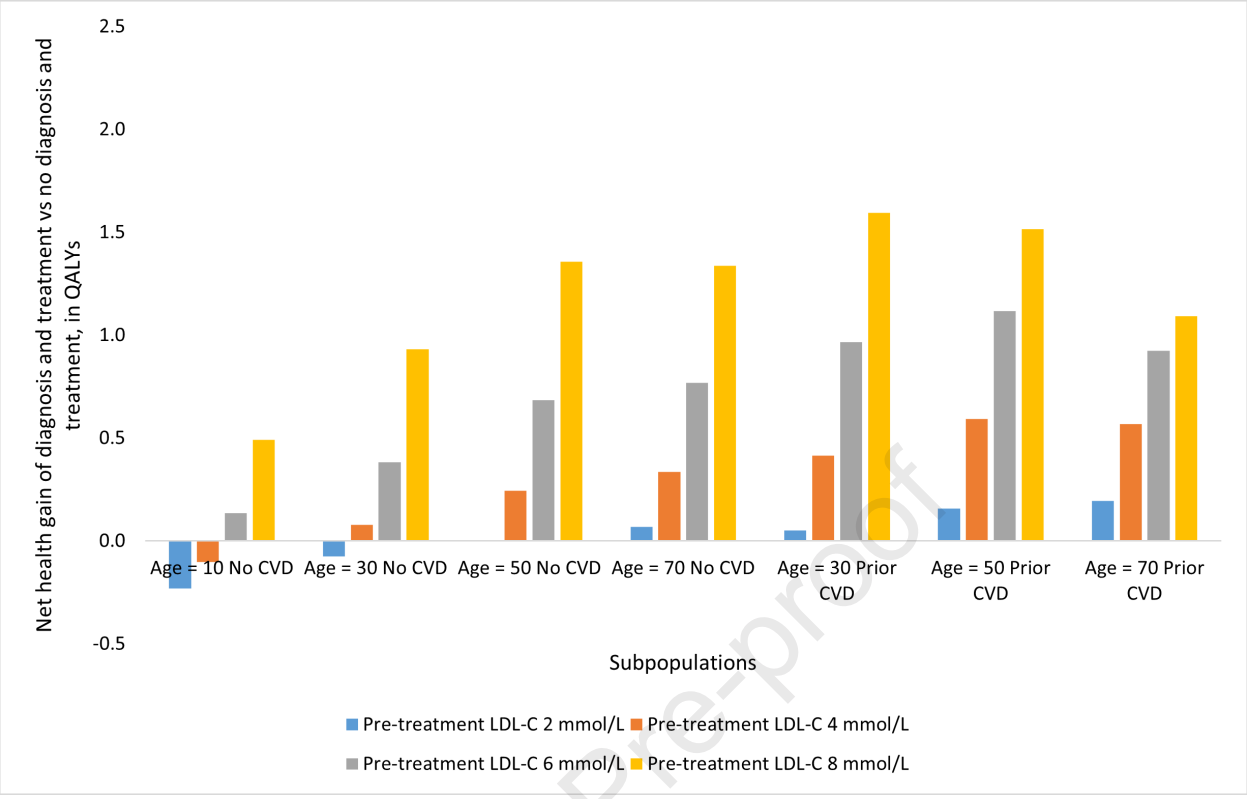


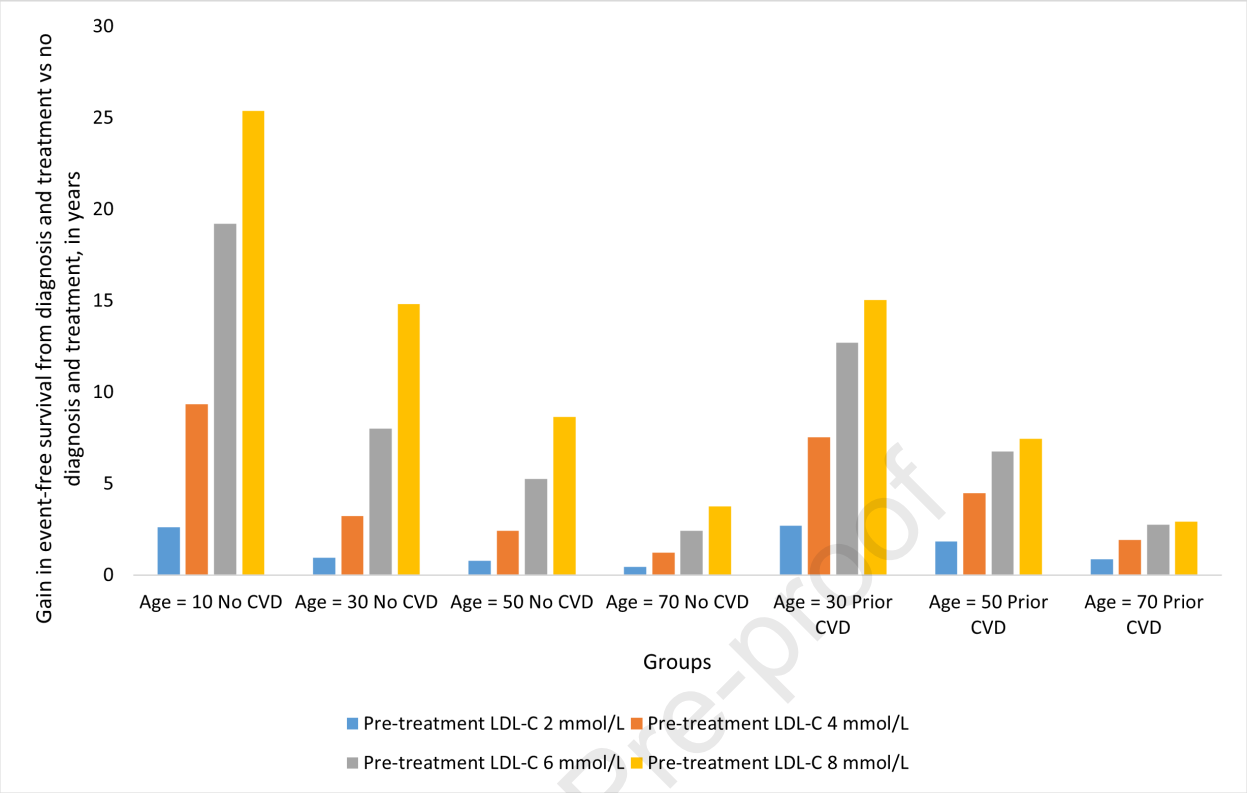
(A) Considering cholesterol burden. (B) Not considering cholesterol burden.

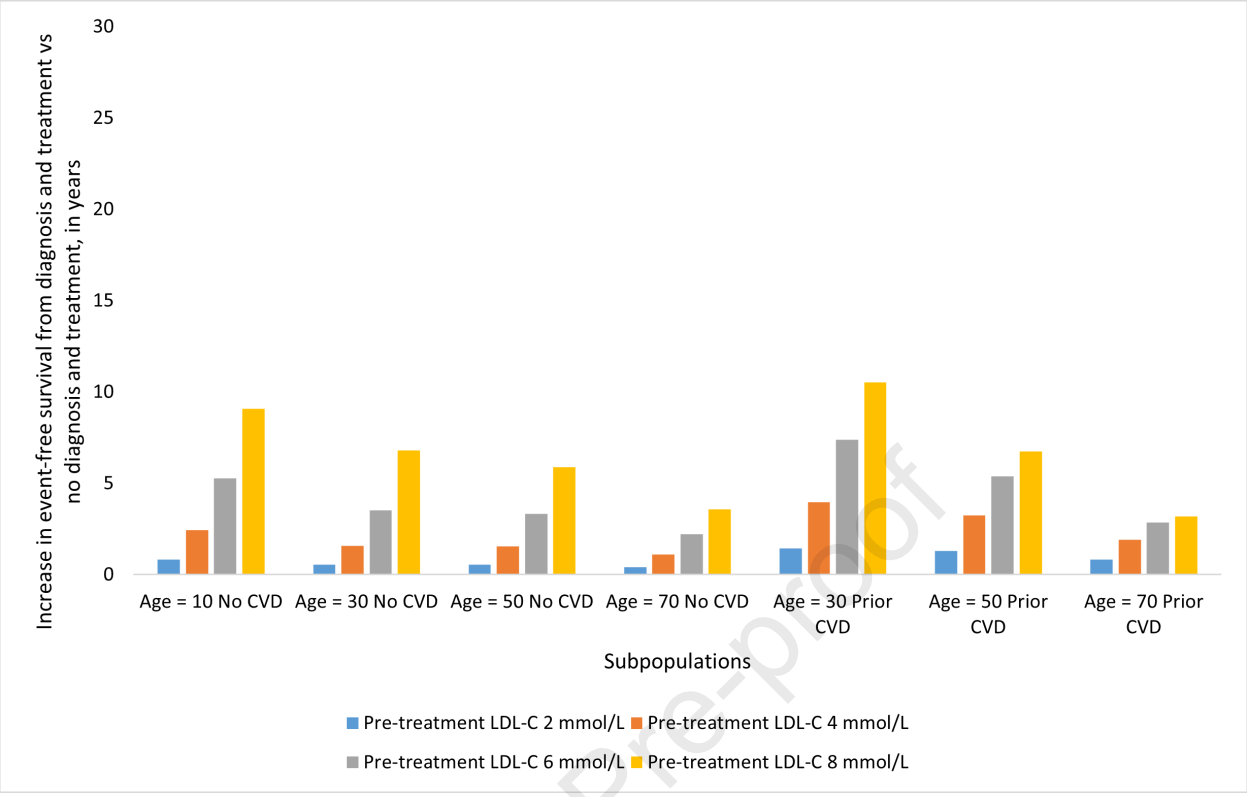
CVD: cardiovascular disease. LDL-C: low density lipoprotein cholesterol. QALY: quality-adjusted life year.











Highlights

- The benefits of diagnosis and treatment of people with familial hypercholesterolaemia are large.
- Considering cholesterol burden in cost-effectiveness modelling shows larger benefits from diagnosis and treatment.
- The magnitude of benefits also depends on prognostic factors, such as age, gender, low-density lipoprotein cholesterol, and cardiovascular disease history.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Rita Faria is currently employed by Astellas Pharma Europe Ltd., however this work was fully conducted before taking up this employment and while being an employee of the University of York.
Stephen Weng was part of an institution that received grants from the NIHR SPCR for research related to Familial Hypercholesterolaemia, consulting fees from his Academic Advisory Committee for Road to Health Ltd, Honoraria and travel fees from Amgen for lectures on familial hypercholesterolaemia, was previously a committee member for the MHRA CPRD Independent Scientific Advisory Committee and is currently employed by Janssen R&D.
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Edward Cox, Pedro Saramago Goncalves, Ralph Akyea, Barbara Iyen and Beth Woods have no conflicts of interest to declare.