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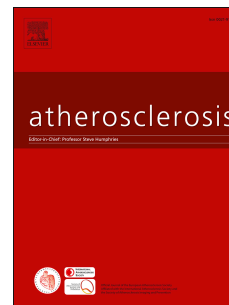
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How does cholesterol burden change the case for investing in familial hypercholesterolaemia? A cost-effectiveness analysis

Rita Faria, Pedro Saramago, Edward Cox, Stephen Weng, Barbara Iyen, Ralph K. Akyea, Steve E. Humphries, Nadeem Qureshi, Beth Woods



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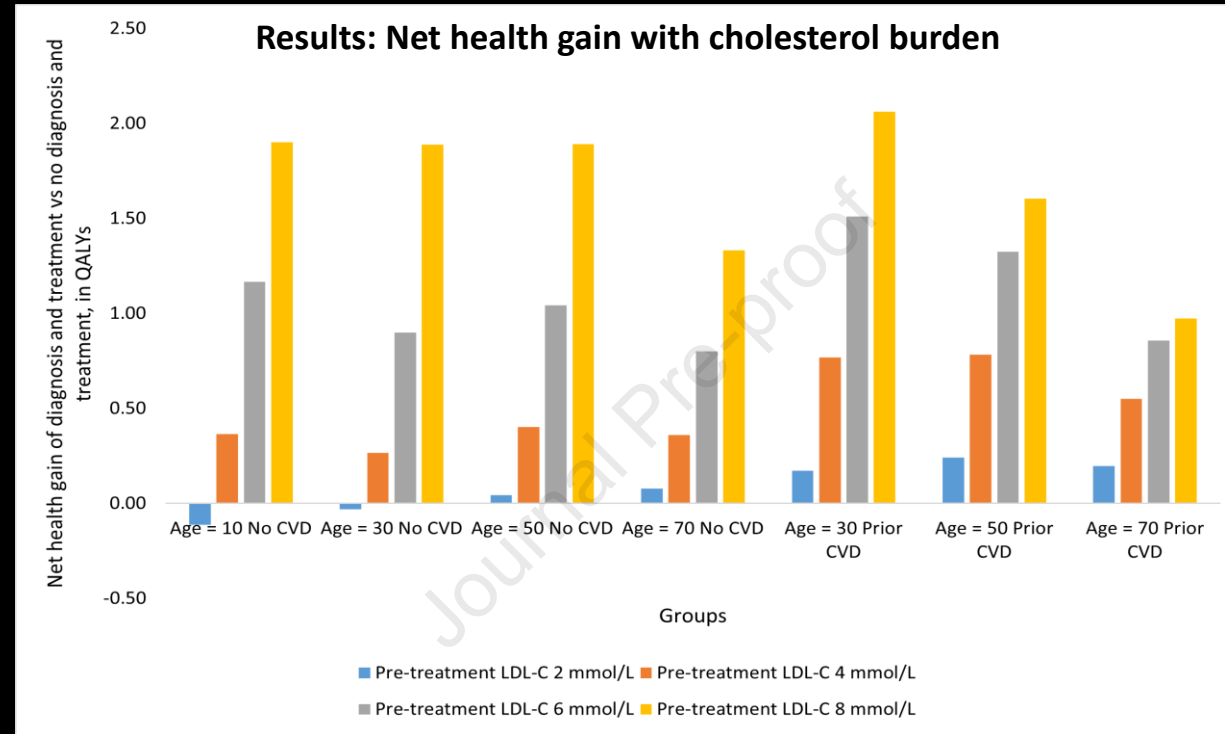
How does cholesterol burden change the case for investing in familial hypercholesterolaemia? A cost-effectiveness analysis

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.

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

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1 Abstract

2 **Background and aims:**

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

7 **Methods:**

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

13 **Results:**

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

19 **Conclusions:**

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

- 1 **Keywords**
- 2 Familial hypercholesterolaemia, cost-effectiveness, cholesterol

Journal Pre-proof

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

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

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

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

17 2.1 Model structure

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

1 2.2 Model inputs

2 2.2.1 Effect of diagnosis on LDL-C and CVD risk

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

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

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

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

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

3 2.2.2 Risk of CVD events and death

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

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

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

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

6 2.2.3 Costs and health-related quality of life

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

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

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

19 Analysis

20 The base-case results are probabilistic, being calculated as the mean over 5,000 Monte Carlo
21 simulations [29]. Model validation is reported in *Supplementary Appendix, Validation*. The
22 sensitivity analysis tested 30 alternative assumptions and model inputs, run deterministically given the
23 similarity between probabilistic and deterministic results (*Supplementary Appendix, Scenario Analysis*
24 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

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

3 Net health gains can be converted into monetary units (to net monetary gains) to understand
4 the magnitude of the investment warranted in diagnosis. As with the net health gains, the investment
5 warranted in diagnosis and treatment varies by subpopulations' prognostic factors and depends on
6 whether cholesterol burden is considered. For example, at the cost-effectiveness threshold of
7 £15,000/QALY, if considering cholesterol burden, the investment warranted can be as little as £663
8 per individual for subpopulations aged 50 years and pre-treatment LDL-C = 2 mmol/L, but
9 approximately £28,000 if pre-treatment LDL-C = 8 mmol/L. If cholesterol burden is not considered, it
10 is £15 per individual for subpopulations aged 50 years and pre-treatment LDL-C = 2 mmol/L and
11 approximately £20,000 if pre-treatment LDL-C = 8 mmol/L (*Supplementary Table 37*).

12 3.2 Secondary outcomes

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

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

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

3 3.3 Uncertainty and scenario analysis

4 Uncertainty related to the assumptions related to the model design and parameterisation were
5 assessed with scenario analysis. The results were robust to most scenarios (*Supplementary Tables 38-*
6 *39*). Irrespective of whether cholesterol burden is considered, the scenario with the greatest impact on
7 the number of subpopulations for whom diagnosis is a positive net health gain is the scenario
8 assuming that those with LDL-C ≤ 2 mmol/L are not actively treated with cholesterol-lowering
9 therapy and have no benefits from diagnosis (nine fewer subpopulations if considering cholesterol
10 burden and eight fewer without cholesterol burden). Scenarios with net health gain from diagnosis
11 was positive in more subpopulations were those where diagnosis and treatment reduced LDL-C to a
12 greater extent than the 33% reduction in the base-case, such as the scenario where diagnosis reduced
13 LDL-C by 50% as per NICE target [2] (compared to 33% reduction in the base-case); and scenarios
14 where the long-term CVD risk was higher than in the base-case (e.g., using the exponential parametric
15 model rather than the generalised gamma model in base-case); and the scenario assuming that
16 monitoring following diagnosis involved fewer medical appointments compared to the base-case. If
17 achieving the NICE recommended target of 50% reduction in LDL-C requires a large increase in
18 treatment costs, gains from diagnosis and treatment are lower (see Online Supplementary Material
19 Figures 26-27 for illustrative scenarios). Probabilistic sensitivity analysis results suggest that
20 parameter uncertainty has a small impact on the decision uncertainty (see *Supplementary Figures 22-*
21 *25*).

22 4. Discussion

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

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

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

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

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

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

13 4.1 Comparison with other studies

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

24 4.2 Limitations

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

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

18 4.3 Conclusion

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

1

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1 Declaration of interests

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

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

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

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

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

20 Author contributions

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

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

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

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

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

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

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

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

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

22 All authors approved the final manuscript.

23

24

25

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20

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1 Tables

2 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	

3

4 ^[a] The European Atherosclerosis Society Consensus Statement equation is

5 $(\exp^{(-0.249 + (\text{number of years of treatment} - 5) \times (-0.0152))})$ [11].

6 CVD: cardiovascular disease. CPRD-FH cohort: cohort of individuals with recorded diagnosis of FH

7 as described in the text. EAS: European Atherosclerosis Society. FH: familial hypercholesterolaemia.

8 LDL-C: low-density lipoprotein cholesterol.

9

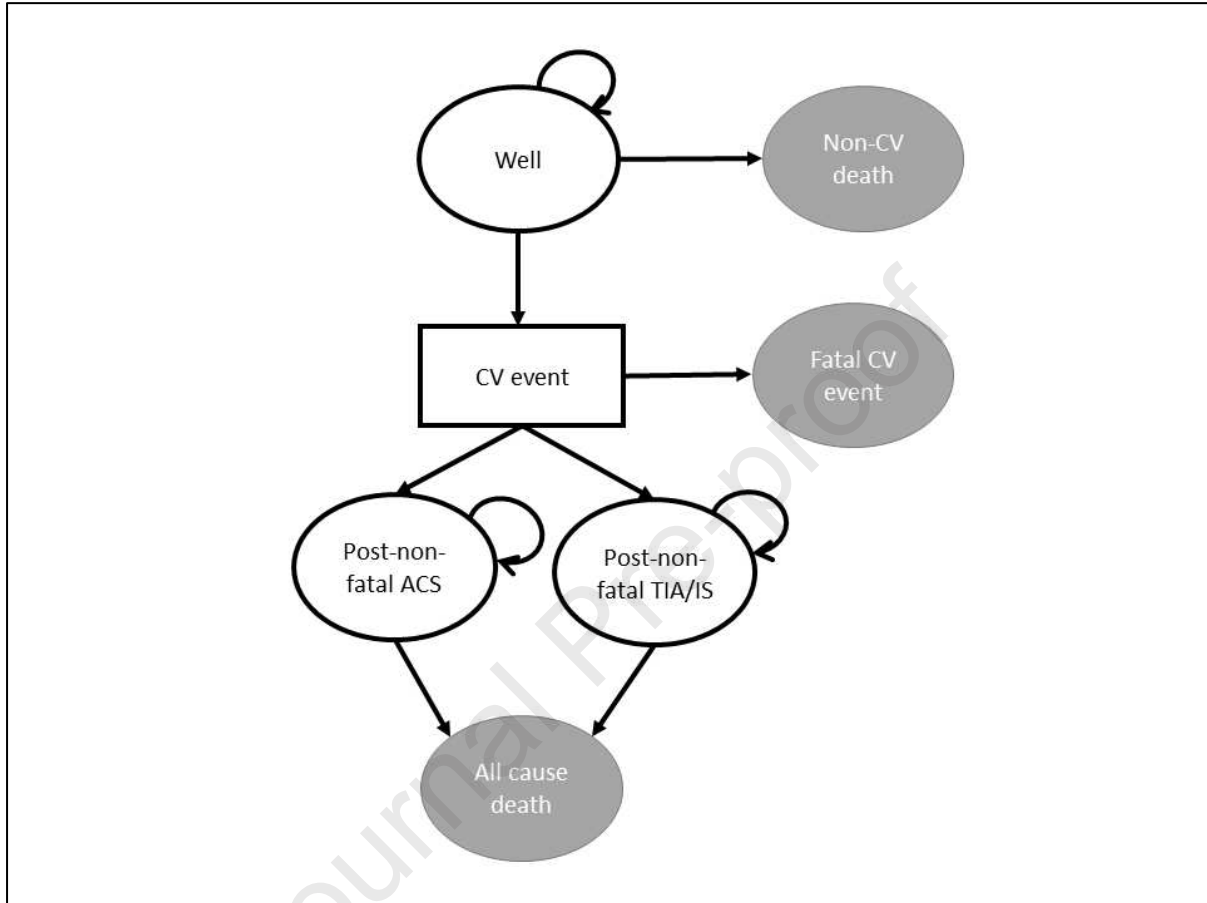
1 Table 2: Monitoring pattern and costs following diagnosis

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

- 2 The base-case assumes that 25% of adult patients are monitored in secondary care, with the remaining
3 being monitored in primary care [26].
- 4 Unit costs were obtained from national sources and inflated to 2019 prices as required [27,28].

1 Figures

2 Figure 1: Model diagram



3

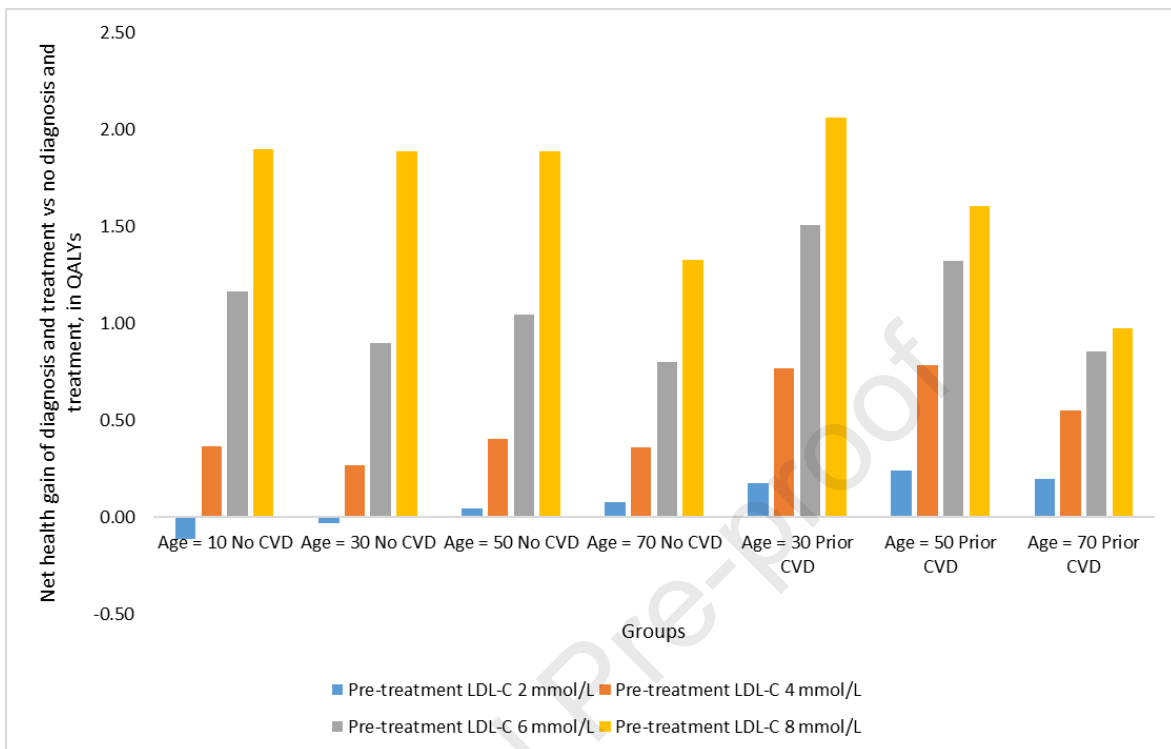
4 Individuals enter the model in the 'well state' at the time of diagnosis and are at risk of a first major
5 cardiovascular event and non- cardiovascular death. Following a non-fatal event, individuals are at
6 risk of all-cause death.

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

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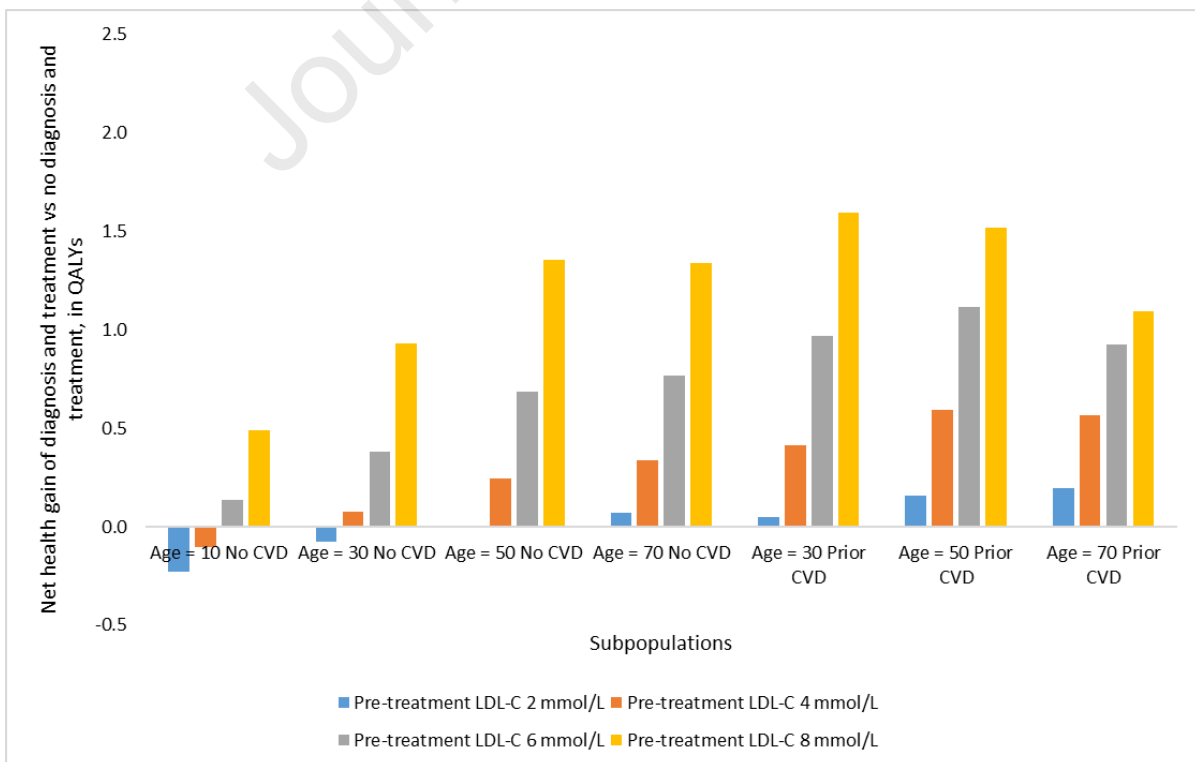
1 Figure 2: Net health gain from diagnosis and treatment

2 (A)



3

4 (B)



5

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

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

8

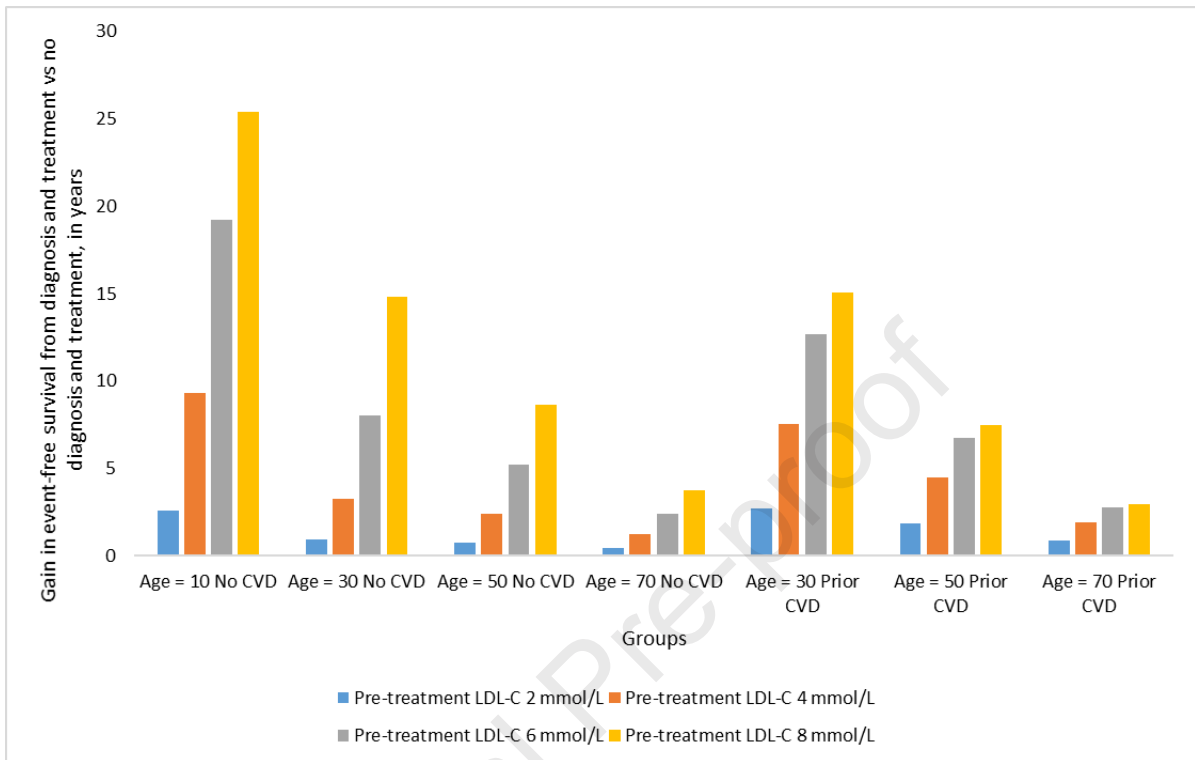
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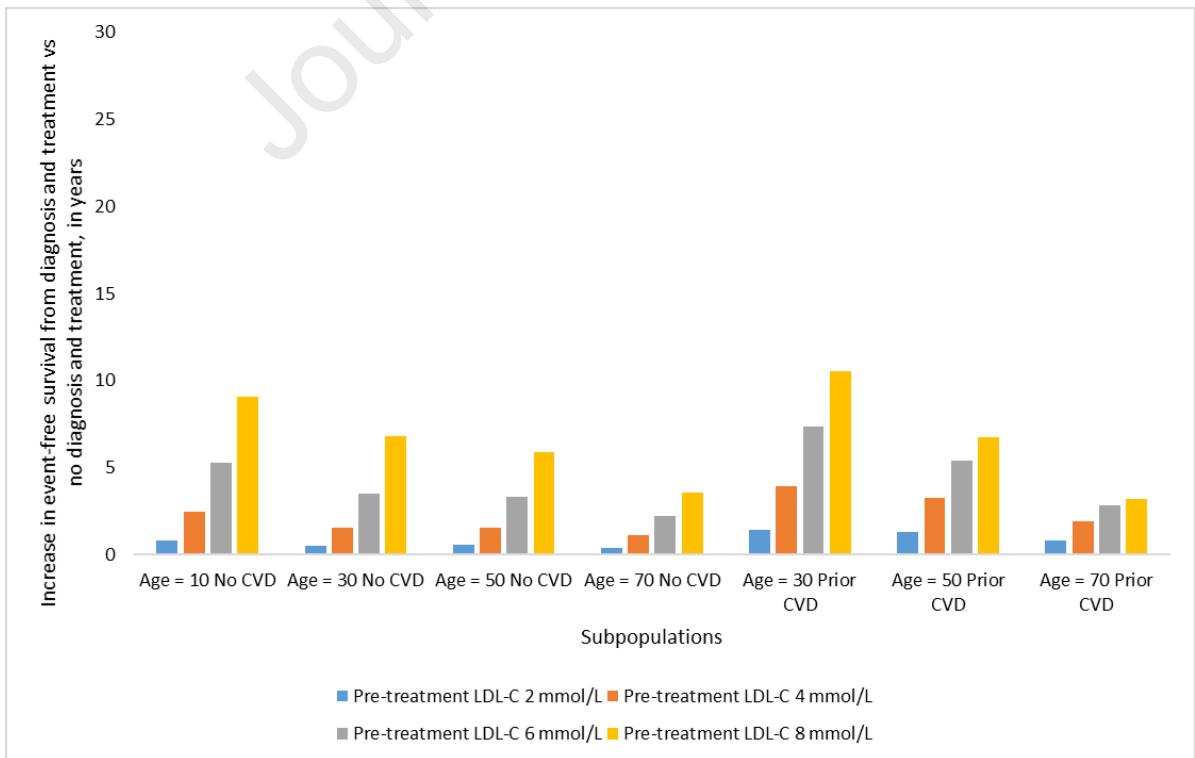
1 Figure 3: Gains in event-free life expectancy from diagnosis and treatment

2 (A)



3

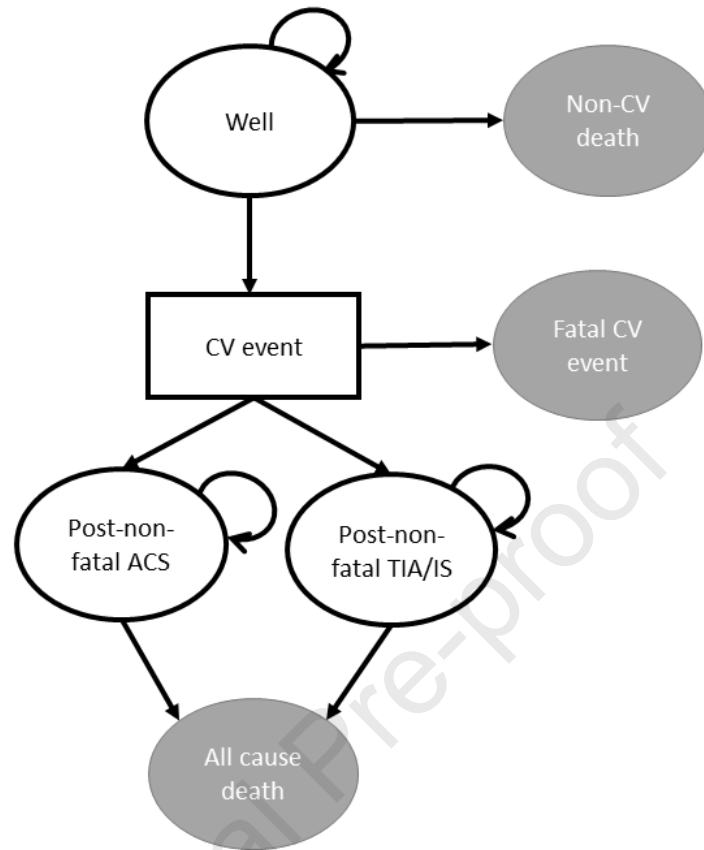
4 (B)

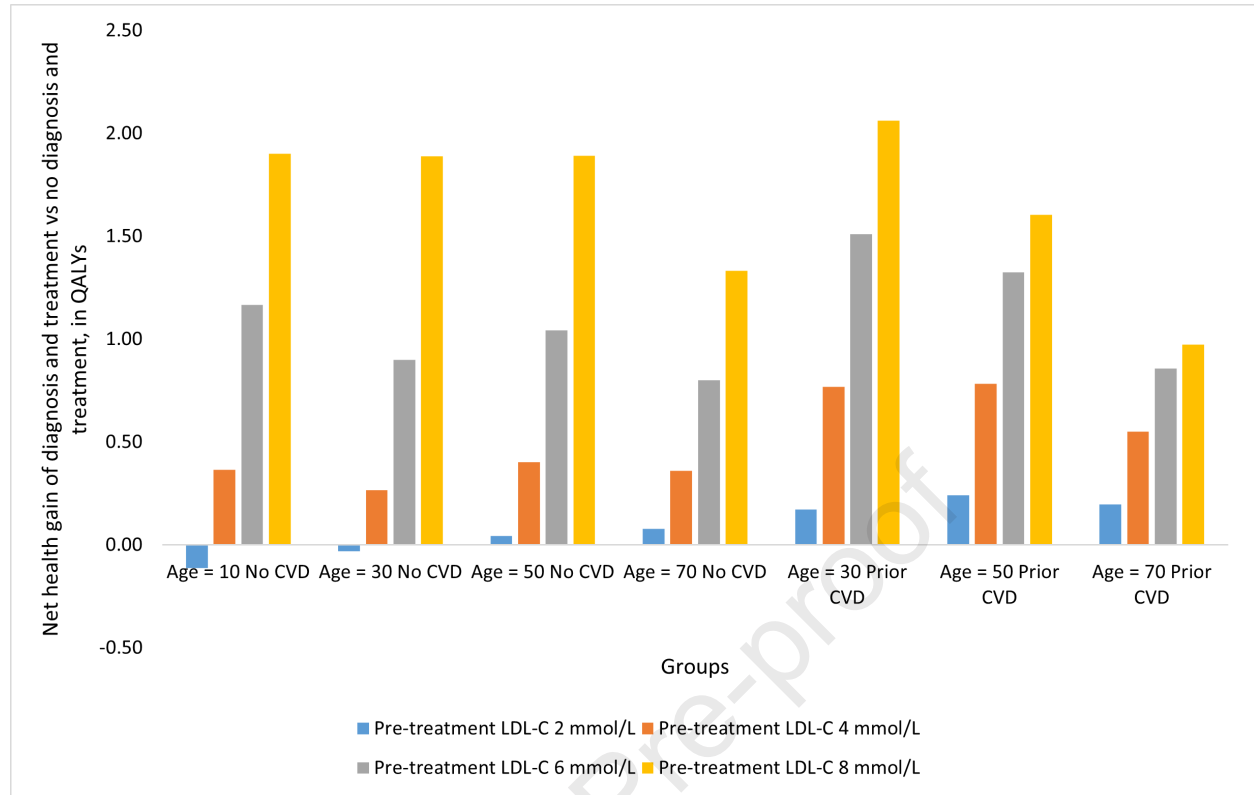


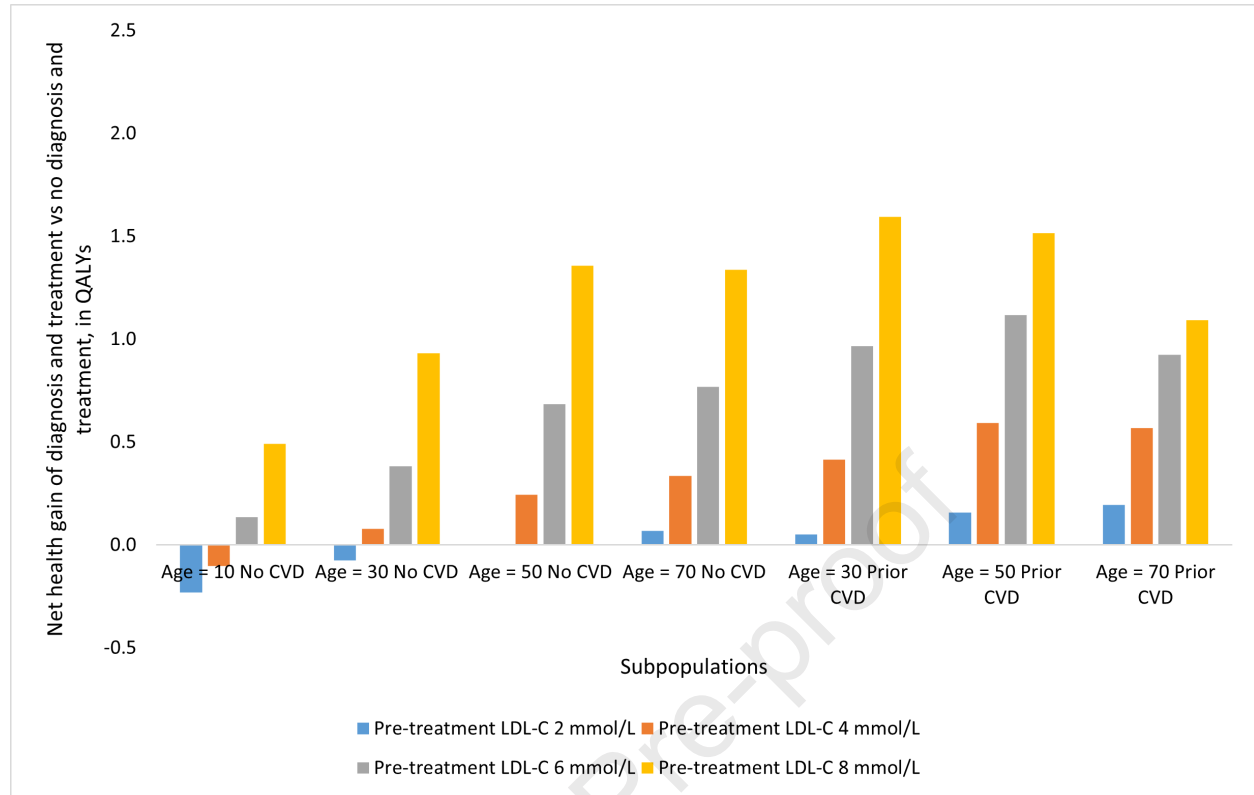
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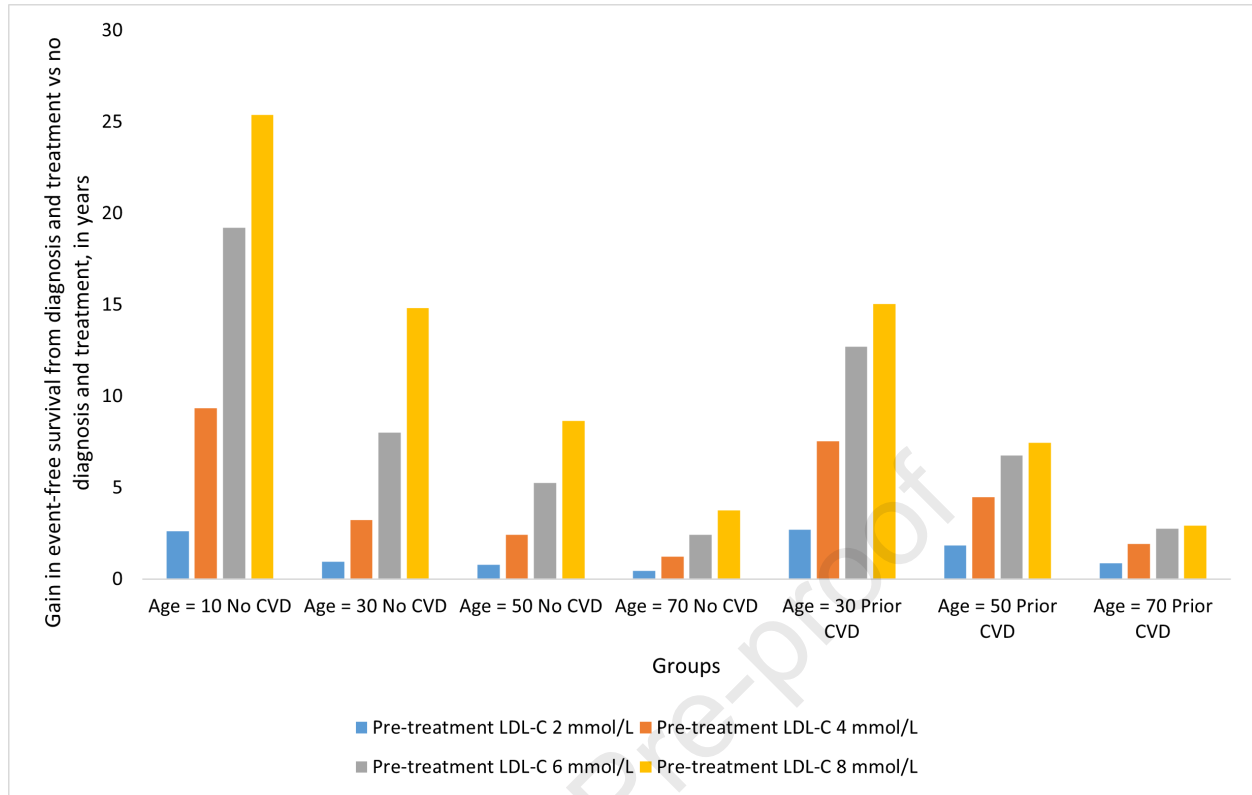
- 1 (A) Considering cholesterol burden. (B) Not considering cholesterol burden.
- 2 CVD: cardiovascular disease. LDL-C: low density lipoprotein cholesterol. QALY: quality-adjusted
- 3 life year.
- 4

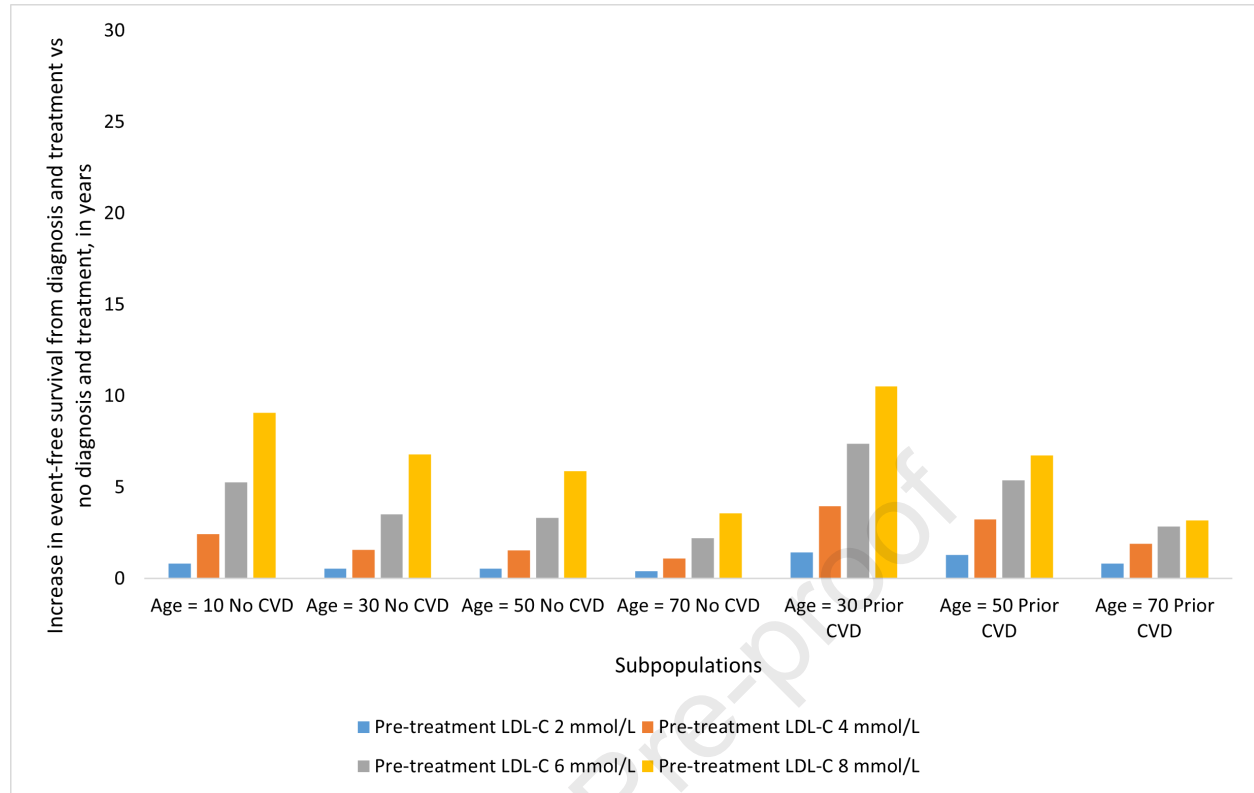
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Highlights

- 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.

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.