

1 *Title Page*

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

4

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1 Abstract

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3 **Background and aims:**

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

8 **Methods:**

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

14 **Results:**

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

20 **Conclusions:**

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

1    **Keywords**

2    Familial hypercholesterolaemia, cost-effectiveness, cholesterol

3    **One sentence summary**

4    The benefits of diagnosis and treatment of familial hypercholesterolaemia are large, but their  
5    magnitude depends on prognostic factors, such as pre-treatment cholesterol level, and importantly on  
6    whether the effect of high cholesterol since birth on the risk of heart disease is considered.

7    **Highlights**

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

14    **Data availability statement**

15    The individual level data underlying this article were provided by the Clinical Practice Research  
16    Datalink and NHS Digital under data sharing agreements specifically for this study. The agreements  
17    in place for use of this data do not permit further distribution or sharing, hence these data cannot be  
18    shared. The cost-effectiveness model will be shared on reasonable request to the corresponding  
19    author.

# 1 Manuscript body

## 2 Introduction

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

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

## 19 Materials and Methods

20           The cost-effectiveness analysis took the perspective of the UK National Health Service  
21 (NHS) at a 2019 price base, and discounting future costs and health benefits to their present value at  
22 3.5% per annum [12].

23           The cost-effectiveness model simulated the outcomes of hypothetical groups of people with  
24 FH, termed “subpopulations”, if they had been diagnosed and treated, and if they had not been  
25 diagnosed and remained untreated until their first CVD event. The subpopulations were defined

1 according to the key prognostic factors of age at diagnosis (10, 30, 50, and 70 years), sex, prior  
2 cardiovascular history, and pre-treatment LDL-C (2, 4, 6, and 8 mmol/L), selected given their impact  
3 on CVD risk [1–3].

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

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

## 18 Model structure

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

## 1 Model inputs

### 2 *Effect of diagnosis on LDL-C and CVD risk*

3 All model inputs are presented in the *Online Supplementary Material List of model inputs*.

4 Table 1 shows the model inputs related to the effect of diagnosis (and treatment) on LDL-C and CVD  
5 risk.

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

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

1           The alternative scenario, without cholesterol burden, assumed that the change in  
2 cardiovascular event risk was unaffected by the duration of treatment and corresponded to the  
3 reduction in major vascular event risk estimated by a large meta-analysis of statin trials at 21% per 1  
4 mmol/L reduction in LDL-C [17].

#### 5 *Risk of CVD events and death*

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

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

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



1 the scenario); (3) applying the reciprocal of this risk reduction to the CVD risk estimated from the  
2 parametric survival analysis for individuals who were diagnosed and treated.

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

#### 8 *Costs and health-related quality of life*

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

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

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

#### 21 Analysis

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

1 similarity between probabilistic and deterministic results (see *Online Supplementary Appendix*  
2 *Scenario Analysis* for details).

### 3 Results

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

#### 6 Primary outcome: net health benefit

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

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

24 The impact of cholesterol burden on net health gain depends on age. For example, the net  
25 health gain in subpopulations aged 10 years with pre-treatment LDL-C = 8 mmol/L is 0.49 QALYs

1 per individual without considering cholesterol burden vs 1.90 QALYs considering cholesterol burden  
2 (approximately 3.8 times larger). In subpopulations aged 50 years with pre-treatment LDL-C = 8  
3 mmol/L, the gain is 1.36 QALYs per individual without considering cholesterol burden vs 1.89  
4 QALYs considering cholesterol burden (39% larger). The difference is more pronounced for younger  
5 subpopulations due to their longer exposure period, hence they have longer to benefit from treatment,  
6 which results in lower LDL-C exposure.

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

## 17 Secondary outcomes

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

1           If cholesterol burden is not considered, event-free life expectancy gain is lower at 0.4-1.1  
2 years per individual across the subpopulations, albeit the pattern is similar to the analysis with  
3 cholesterol burden (see Figure 4B). Life expectancy and quality-adjusted life expectancy gains are  
4 also lower at up to 4 years and 4 QALYs per individual respectively (see *Online Supplementary*  
5 *Appendix Figures 19-20*). Diagnosis and treatment results in cost savings to the NHS in  
6 subpopulations who have pre-treatment LDL-C  $\geq 8$  mmol/L, if pre-treatment LDL-C  $\geq 6$  mmol/L if  
7 aged  $\geq 50$  years of age, and if pre-treatment LDL-C  $\geq 4$  mmol/L if with CVD history (see *Online*  
8 *Supplementary Appendix Figure 21*).

## 9   Uncertainty and Scenario analysis

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

# 1 Discussion

2 This study is the first to estimate the net health gain of diagnosing and treating individuals  
3 with FH, depending on prognostic factors, and with and without considering the impact of including  
4 cholesterol burden. CVD risk and LDL-C response to treatment were estimated from routinely  
5 collected data of individuals with FH in England, which subsequently informed a new cost-  
6 effectiveness model. The cost-effectiveness model included key prognostic factors, namely pre-  
7 treatment LDL-C, age at diagnosis, gender, and CVD history, which allowed for the estimation of  
8 subpopulation-specific long-term health outcomes, costs, and net health gain. These results can inform  
9 the design of policies for diagnosis that target individuals with different characteristics (e.g., cascade  
10 screening versus universal screening with LDL-C in childhood). Furthermore, the cost-effectiveness  
11 model can be easily adapted to evaluate new drugs and treatment policies which may increase LDL-C  
12 reductions but have greater costs, as well as to use inputs from other countries (e.g., unit costs,  
13 management practices) to provide country-specific results.

14 Diagnosis and treatment of individuals with FH generally leads to large net health gains for  
15 the NHS. That is, given the health benefits to people with FH and the impact on NHS costs, it is cost-  
16 effective to diagnose and treat most individuals with FH over specific LDL-C levels (individuals with  
17 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  
18 with CVD history). This means that there is scope for investment in better diagnosis and potentially  
19 more intensive (and effective) treatment strategies). The large magnitude of net health gains suggests  
20 that investment in infrastructure for more diagnosis and treatment are likely to be good value for  
21 money to the NHS.

22 Cholesterol burden is a major driver of cost-effectiveness results, whilst its magnitude being a  
23 key uncertainty. In the cost-effectiveness model, cholesterol burden was explicitly incorporated using  
24 the European Atherosclerosis Society Consensus Statement equation [11]. This equation was based on  
25 reviews of studies mostly from individuals without FH, hence its generalisability to individuals with  
26 FH is uncertain. When cholesterol burden was not considered, the effect of LDL-C on cardiovascular

1 risk was constant over time and based on a large meta-analysis of statin trials [17]. However, the trials  
2 had a relatively short follow-up, while cholesterol burden effects may be clearer over a long follow-  
3 up. If cholesterol burden is underestimated or not included, more costly and more effective diagnostic  
4 and treatment policies may, incorrectly, not be recommended. This will affect mostly younger  
5 individuals with FH, given the results of this study that, if cholesterol burden was not considered, the  
6 difference in the magnitude of net health gains was larger in younger subpopulations. For these  
7 reasons, further research is required to quantify the long-term effect of reductions in LDL-C on  
8 cardiovascular risk in individuals with FH and methods to incorporate those effects in cost-  
9 effectiveness modelling.

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

## 18 Comparison with other studies

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

1 levels if cholesterol burden is included and 0-1.36 QALYs if not, hence the Crosland et al estimates  
2 are broadly in the midpoint of the present estimates.

### 3 Limitations

4 The limitations stem mostly from the limitations of the data used to inform the cost-  
5 effectiveness model. Although the CPRD-FH was reasonably large (N=2,135), the number of events  
6 precluded the estimation of risk of recurrent events. Therefore, the estimation of risk of death  
7 following a non-fatal cardiovascular event, which was based on a study in individuals mostly without  
8 FH [20]. Furthermore, younger individuals and individuals with lower pre-treatment LDL-C were  
9 under-represented in the CPRD-FH cohort, increasing the uncertainty around the model results for  
10 younger groups and those with pre-treatment LDL-C = 2 mmol/L. It was not feasible to differentiate  
11 between homozygous and heterozygous FH, hence these results may not generalise to people with  
12 homozygous FH. Due to the sparse data beyond 10 years, the extrapolation of long-term  
13 cardiovascular risk had limited face validity, hence the adjustment using an external study in  
14 individuals with the FH phenotype [19]. Additionally, there is some uncertainty about the extent to  
15 which the coding of individuals in primary care is accurate and complete, hence the generalisability of  
16 the CPRD-FH cohort to individuals with FH. This analysis compared diagnosis and treatment to the  
17 absence of diagnosis and no treatment, however some individuals may be treated, albeit suboptimally,  
18 in the absence of diagnosis. Other uncertainties relate to the effect of diagnosis and treatment on LDL-  
19 C and on costs of monitoring post-diagnosis, given the variability in management practices across the  
20 country and over time, and individual LDL-C response. It was outside the scope of this study to  
21 investigate the relationship between the effectiveness of treatment in reducing LDL-C and its intensity  
22 (hence its costs).

### 23 Conclusion

24 Diagnosis and treatment of individuals with FH results in large net health gains, hence large  
25 scope for investment in diagnosis by the NHS, not only to support diagnosis and treatment but also in  
26 infrastructure and organisation. The magnitude of gains depends on prognostic factors, particularly

1 pre-treatment LDL-C, age at diagnosis, and cardiovascular history. Most importantly, on whether the  
2 increased effect of exposure to raised LDL-C levels on cardiovascular risk, termed cholesterol burden,  
3 is considered. Given their impact on net health gain, future evaluations of policies for the diagnosis  
4 and treatment of individuals with FH should explicitly consider the effect of these prognostic factors  
5 and of cholesterol burden. Further research should explore approaches to quantify cholesterol burden  
6 in individuals with FH.

7

8



## 1 Conflict of interest

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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- 14



# 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 <sup>33</sup>
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 Abbreviations: CVD: Cardiovascular Disease. CPRD-FH cohort: cohort of individuals with recorded

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

8 hypercholesterolaemia. LDL-C: low-density lipoprotein cholesterol.

9

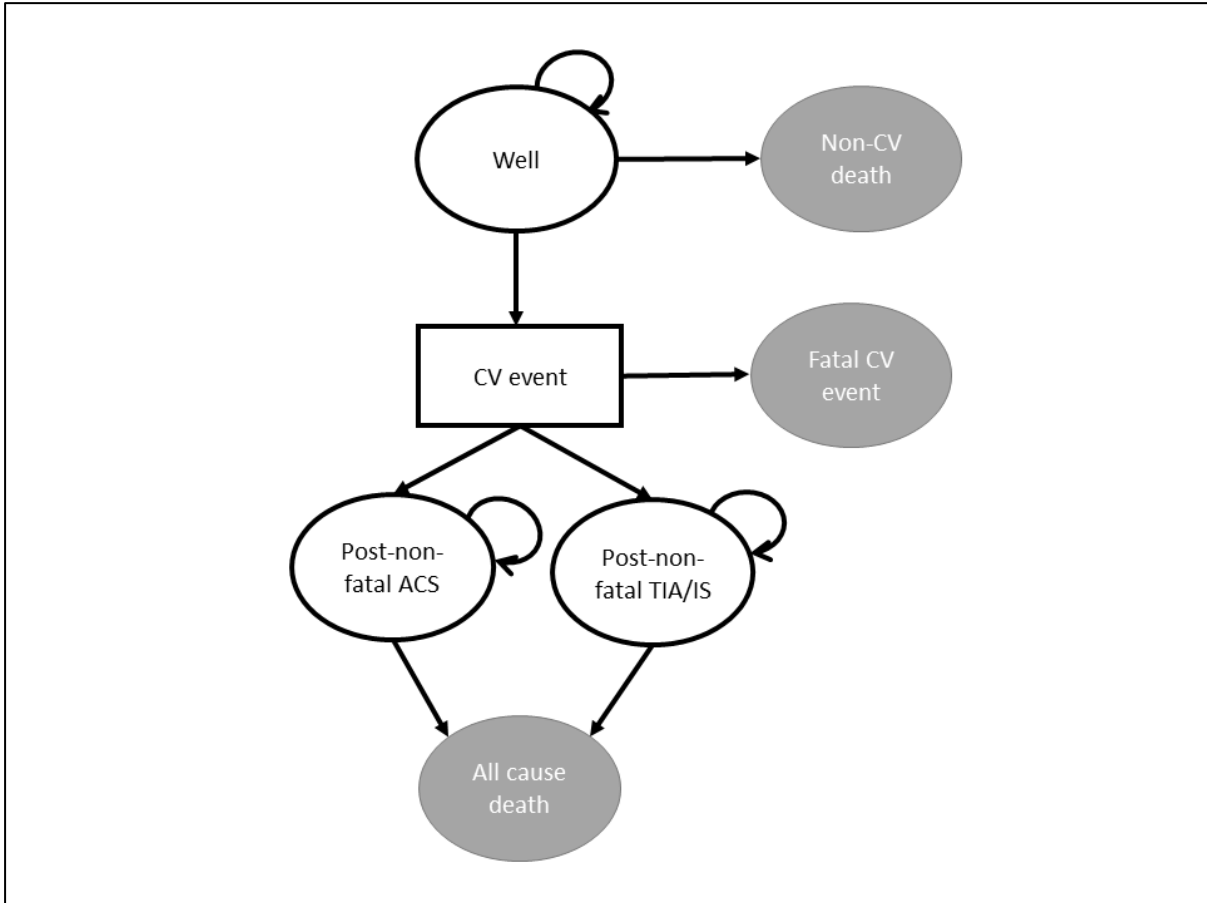
1 *Table 2: Monitoring pattern and costs following diagnosis*

Monitoring and treatment	Number of appointments per year	Mean cost per year
<b>Adults</b>		
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
<b>Children and adolescents</b>		
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

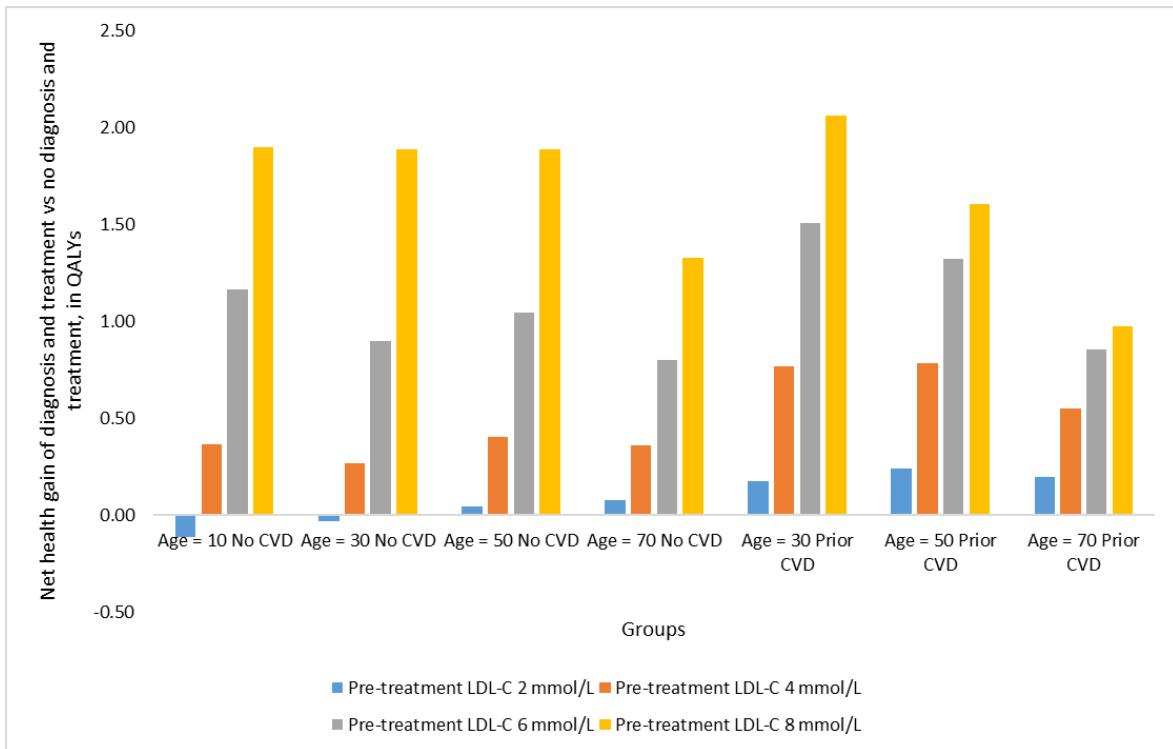
4 Individuals enter the model in the ‘well state’ at the time of diagnosis and are at risk of a first major  
5 cardiovascular event and non- cardiovascular death. Following a non-fatal event, individuals are at  
6 risk of all-cause death.

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

9

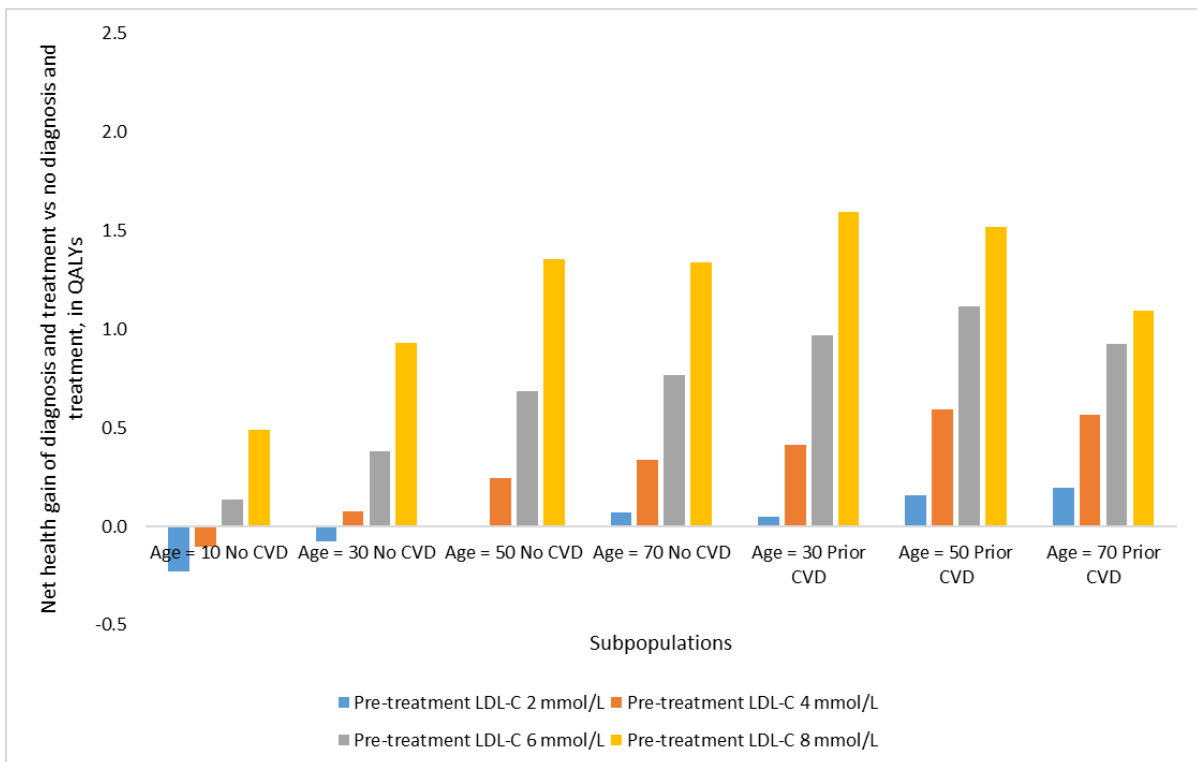
1 *Figure 2: Net health gain from diagnosis and treatment*

2 (A)



3

4 (B)



5

1 QALYs: Quality-adjusted life years.

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

6 (A): Considering cholesterol burden.

7 (B): Not considering cholesterol burden.

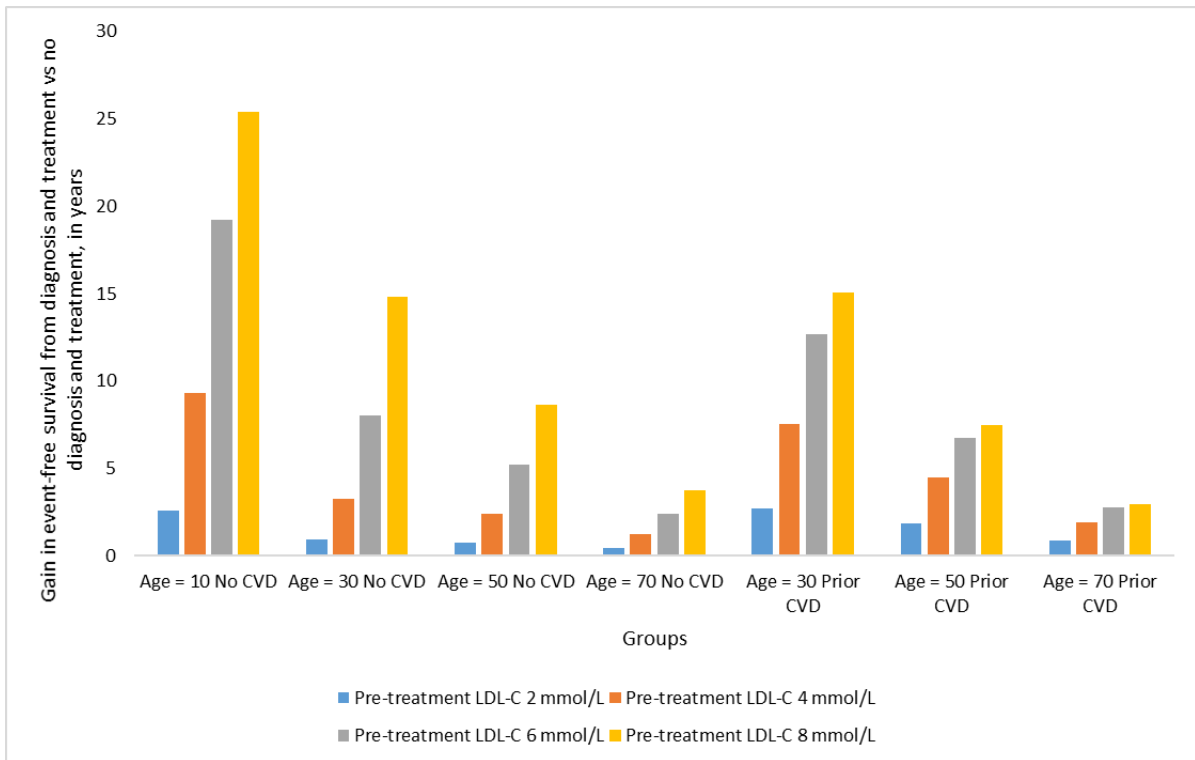
8 Abbreviations: CVD: Cardiovascular disease. LDL-C: low density lipoprotein cholesterol. QALY:  
9 quality-adjusted life year.

10

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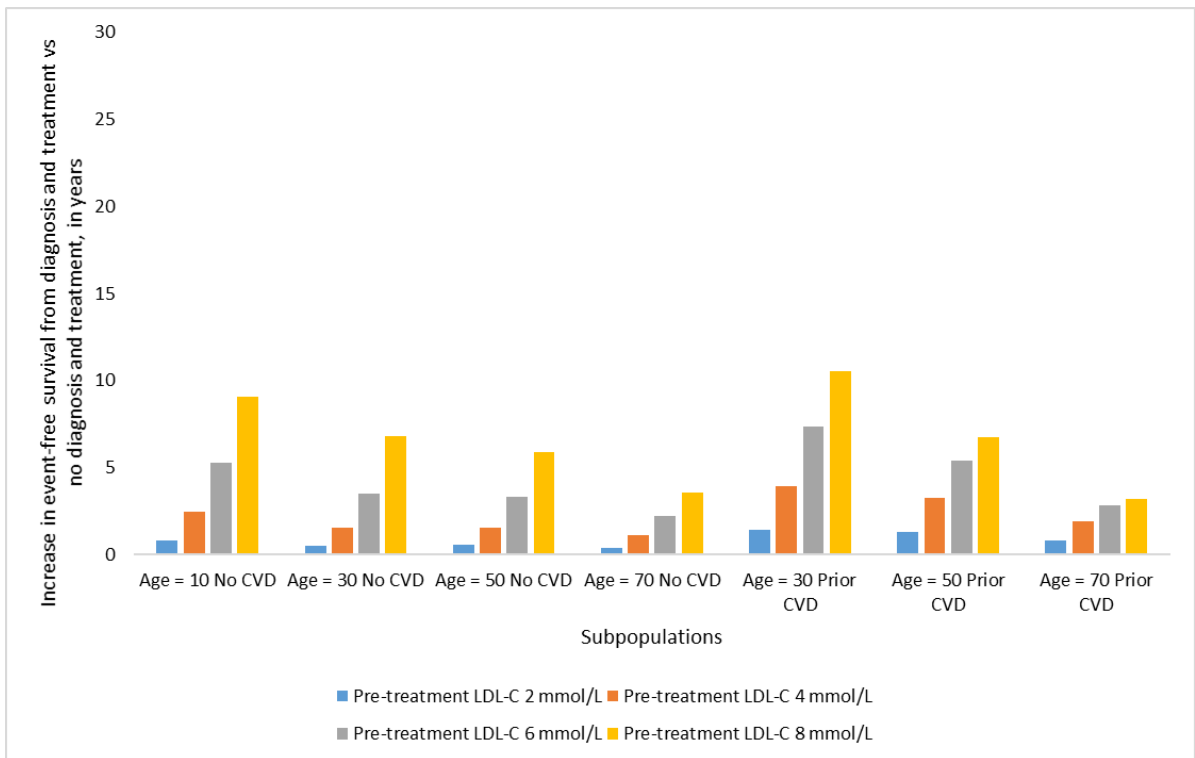
1 *Figure 3: Gains in event-free life expectancy from diagnosis and treatment*

2 (A)



3

4 (B)



5

1 (A): Considering cholesterol burden.

2 (B): Not considering cholesterol burden.

3 Abbreviations: CVD: Cardiovascular disease. LDL-C: low density lipoprotein cholesterol. QALY:

4 quality-adjusted life year.

5