Association of BMI, lipid-lowering medication, and age with prevalence of type 2 diabetes in adults with heterozygous familial hypercholesterolaemia: a worldwide cross-sectional study

*European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration (EAS FHSC)**

Summary

Background Statins are the cornerstone treatment for patients with heterozygous familial hypercholesterolaemia but research suggests it could increase the risk of type 2 diabetes in the general population. A low prevalence of type 2 diabetes was reported in some familial hypercholesterolaemia cohorts, raising the question of whether these patients are protected against type 2 diabetes. Obesity is a well known risk factor for the development of type 2 diabetes. We aimed to investigate the associations of known key determinants of type 2 diabetes with its prevalence in people with heterozygous familial hypercholesterolaemia.

Methods This worldwide cross-sectional study used individual-level data from the EAS FHSC registry and included adults older than 18 years with a clinical or genetic diagnosis of heterozygous familial hypercholesterolaemia who had data available on age, BMI, and diabetes status. Those with known or suspected homozygous familial hypercholesterolaemia and type 1 diabetes were excluded. The main outcome was prevalence of type 2 diabetes overall and by WHO region, and in relation to obesity (BMI ≥30·0 kg/m²) and lipid-lowering medication as predictors. The study population was divided into 12 risk categories based on age (tertiles), obesity, and receiving statins, and the risk of type 2 diabetes was investigated using logistic regression.

Findings Among 46 683 adults with individual-level data in the FHSC registry, 24 784 with heterozygous familial hypercholesterolaemia were included in the analysis from 44 countries. 19 818 (80%) had a genetically confirmed diagnosis of heterozygous familial hypercholesterolaemia. Type 2 diabetes prevalence in the total population was 5·7% (1415 of 24 784), with 4·1% (817 of 19 818) in the genetically diagnosed cohort. Higher prevalence of type 2 diabetes was observed in the Eastern Mediterranean (58 [29·9%] of 194), South-East Asia and Western Pacific (214 [12·0%] of 1785), and the Americas (166 [8·5%] of 1955) than in Europe (excluding the Netherlands; 527 [8·0%] of 6579). Advancing age, a higher BMI category (obesity and overweight), and use of lipid-lowering medication were associated with a higher risk of type 2 diabetes, independent of sex and LDL cholesterol. Among the 12 risk categories, the probability of developing type 2 diabetes was higher in people in the highest risk category (aged 55–98 years, with obesity, and receiving statins; OR 74·42 [95% CI 47·04–117·73]) than in those in the lowest risk category (aged 18–38 years, without obesity, and not receiving statins). Those who did not have obesity, even if they were in the upper age tertile and receiving statins, had lower risk of type 2 diabetes (OR 24·42 [15·57–38·31]). The corresponding results in the genetically diagnosed cohort were OR 65·04 (40·67–104·02) for those with obesity in the highest risk category and OR 20·07 (12·73–31·65) for those without obesity.

Interpretation Adults with heterozygous familial hypercholesterolaemia in most WHO regions have a higher type 2 diabetes prevalence than in Europe. Obesity markedly increases the risk of diabetes associated with age and use of statins in these patients. Our results suggest that heterozygous familial hypercholesterolaemia does not protect against type 2 diabetes, hence managing obesity is essential to reduce type 2 diabetes in this patient population.

Funding Pfizer, Amgen, MSD, Sanofi-Aventis, Daiichi-Sankyo, and Regeneron.

Lancet Diabetes Endocrinol 2024; 12: 811–23

Published Online October 4, 2024 https://doi.org/10.1016/S2213-8587(24)00221-3

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See Online for appendix

Introduction

Heterozygous familial hypercholesterolaemia is a common autosomal dominant condition affecting one in 311 individuals worldwide,[1] characterised by defects in cholesterol-related genes, resulting in reduced clearance of LDL.[2] Phenotypically, this results in high plasma LDL cholesterol with increased risk of atherosclerotic cardiovascular disease.[3] Statins which underpin the lowering of LDL cholesterol have been associated with increased risk of type 2 diabetes in patients without familial hypercholesterolaemia, possibly due to pancreatic lipotoxicity resulting from increased LDL uptake via

Research in context

Evidence before this study

We searched PubMed for articles on the prevalence of type 2 diabetes in heterozygous familial hypercholesterolaemia published in PubMed from database inception to Jan 15, 2024, combining the following search terms or synonyms: "familial hypercholesterolaemia", "diabetes", "body-mass index", "obesity", "age", "lipid-lowering", AND/OR "statins". Additional articles were sought from reference lists of eligible articles. National-level studies reported low prevalence of type 2 diabetes in Dutch and Spanish cohorts with genetic confirmation of heterozygous familial hypercholesterolaemia relative to unaffected family members, and in Canadian cohorts compared with the general population of similar age, leading to the hypothesis that those with heterozygous familial hypercholesterolaemia might be less susceptible to type 2 diabetes. Notably, in these studies, prevalence of known risk factors for type 2 diabetes seemed low in well-managed patients with early age of detection, hence modification and maintenance of favourable lifestyle factors rather than heterozygous familial hypercholesterolaemia might be the reason for the lower prevalence. Other national-level studies were also done only in European and North American populations. Type 2 diabetes accounts for more than 90% of diabetes cases worldwide and prevalence differs in each International Diabetes Federation region, which might also be the case for heterozygous familial hypercholesterolaemia, but global data remain scarce.

Added value of this study

Pooling data from different world regions would allow to test the assumption that a low prevalence of type 2 diabetes in heterozygous familial hypercholesterolaemia is generalisable globally and uninfluenced by demographic characteristics associated with type 2 diabetes, with greater statistical power than previously feasible. The European Atherosclerosis Society Familial Hypercholesterolaemia Studies Collaboration registry provides data on every WHO region, which has been standardised to a data dictionary and harmonised into a single global database. In our study on around 25 000 adults with heterozygous familial hypercholesterolaemia from 44 countries, the prevalence of type 2 diabetes was 5·7% overall, with the highest regional prevalence in the Eastern Mediterranean and lowest in Europe, which is similar to the prevalence of type 2 diabetes in the general population reported by the International Diabetes Federation. We also found that the same factors that increase diabetes risk in the general population, namely overweight and obesity, statin use, and advancing age, are associated with higher odds of type 2 diabetes in this large cohort of patients with heterozygous familial hypercholesterolaemia. Even in the group of patients in the top age tertile and receiving statins, who inevitably have a higher risk of diabetes, being non-obese was associated with substantially lower odds of diabetes than in those who are obese. This finding suggests that the risk of diabetes might be markedly attenuated in these patients if obesity is addressed.

Implications of all the available evidence

In individuals with heterozygous familial hypercholesterolaemia, obesity, statin therapy, and advancing age were associated with a higher risk of type 2 diabetes (with obesity showing the strongest association), suggesting that known risk factors of diabetes in the general population are equally applicable to these individuals. Given the importance of statins and long nature of treatment required to reduce the high lifetime risk of atherosclerotic cardiovascular disease, shared decision making between the treating physician and the patient should highlight that, compared with obesity, the adverse effects of statins on the risk of type 2 diabetes are modest.

the LDL receptor. However, studies from the Netherlands, Spain, and Canada,[4–6] where screening and management of heterozygous familial hypercholesterolaemia is more thorough than in other parts of the world, have reported low prevalence of type 2 diabetes in this population, leading to speculation that heterozygous familial hypercholesterolaemia might be protective against the risk of type 2 diabetes.

Type 2 diabetes accounts for more than 90% of diabetes cases worldwide, but prevalence differs by International Diabetes Federation regions in the general population.[7] If heterozygous familial hypercholesterolaemia was protective against type 2 diabetes, then the prevalence of type 2 diabetes would be expected to be similar across regions, but data remain scarce. Studying the global cohort, including demographic characteristics underrepresented in previous studies, offers an opportunity to further evaluate the assumption that heterozygous familial hypercholesterolaemia might reduce susceptibility to type 2 diabetes with greater precision than previously feasible. If the prevalence of type 2 diabetes was higher than historical estimates, then we could study whether some of the determinants of type 2 diabetes in the general population were applicable to those with heterozygous familial hypercholesterolaemia.

The aim of our study was to investigate the associations of known key determinants of type 2 diabetes (such as BMI, lipid-lowering medication [statin *vs* non-statin], and age) with its prevalence in people with heterozygous familial hypercholesterolaemia.

Methods

Study design and participants

In this worldwide cross-sectional study, we used individual-level data from the global European Atherosclerosis Society-Familial Hypercholesterolaemia

Studies Collaboration (EAS-FHSC) registry.[8,9] The FHSC registry includes adults and children with a clinical or genetic diagnosis (or both) of heterozygous or homozygous familial hypercholesterolaemia.[8,9] Adults older than 18 years with a clinical or genetic diagnosis of heterozygous familial hypercholesterolaemia who had data available on age, BMI, and diabetes status were included in the present study. For those with a clinical diagnosis, only those with probable or definite diagnosis by Dutch Lipid Clinic Network criteria (possible or definite in case of Simon–Broome criteria) were included. Those with known or suspected homozygous familial hypercholesterolaemia (LDL cholesterol ≥12·9 mmol/L [≥500 mg/dL] or having undergone lipoprotein apheresis, or both); or with type 1 diabetes were excluded. Participants without a specified type of diabetes were assumed to have type 2 diabetes, given that type 2 accounts for most cases worldwide[7] and only adults were included.

The EAS FHSC registry protocol[9] (ClinicalTrials.gov, NCT04272697) is approved by the Joint Research Compliance Office and Imperial College Research Ethics Committee (Imperial College London, London, UK). All FHSC National Lead Investigators contributing data provided written confirmation of sharing data in compliance with local ethical policies and regulations. Methods of compiling and managing the registry have been described previously.[8,9]

Procedures

Clinical and laboratory data were supplied by the individual investigators, as measured locally in the respective clinics and laboratories. The main outcome was prevalence of type 2 diabetes overall and by WHO region,[10] and in relation to obesity and lipid-lowering medication as predictors. Africa was included only in the pooled global data, but not in region-specific analysis due to the small sample size. The Netherlands was reported separately from Europe. South-East Asia and Western Pacific regions were pooled for the analysis. BMI categories were defined by WHO cutoffs.[11] There were six (<1%) underweight participants (BMI <18·5 kg/m²) with diabetes and 479 (2·0%) without diabetes, so we combined underweight with healthy weight in all models. Lipid-lowering medication were reported by type and dose, as previously described.[8] 1904 (7·7%) individuals were receiving the highest dose of atorvastatin 80 mg or rosuvastatin 40 mg, herein referred to as the highest potency statin group.

Statistical analysis

Power calculations, done using R pwr package (version 1.3–0), indicated that the power afforded by our sample size to detect 10% higher chance of type 2 diabetes per increased BMI category, adjusted for age at α=0·05, was 0·97 in the total cohort (n=24784) and 0·94 in the genetically diagnosed cohort (n=19 818).

Categorical variables were reported as absolute numbers and relative frequencies and compared in participants with and without diabetes using Pearson's χ^2 test. Continuous variables for population characteristics were reported as mean (SD) or median (IQR), and compared using an independent *t* test or Mann–Whitney *U* test. Descriptive estimates of age are given as median (5th and 95th percentiles) for a broader view of the distribution.

Multivariable logistic regression was used to determine the independent associations of BMI category and lipid-lowering medication as predictors, with type 2 diabetes as the outcome. We generated a directed acyclic graph to identify potential confounders for inclusion in the models (appendix p 27). Model one was adjusted for age and sex and model two was additionally adjusted for LDL cholesterol. The linearity assumption for the continuous predictor versus logit of the outcome was verified by applying the Box–Tidwell procedure. The proportion of patients with missing data for at least one predictor was 867 (3·5%) of 24784 in model one and 6691 (27%) of 24784 in model two. To address missing data, we used multiple imputation via predictive mean matching using the R mice package (version 3.16.0). This procedure incorporated all covariates, country and region, and generated 20 imputed datasets, to which logistic regression was applied for the primary analysis. We also ran this analysis using the original (non-imputed) dataset. In a prespecified sensitivity analyses, we only included those with type 2 diabetes and excluded those with diabetes-type not specified. The study population was divided into 12 risk categories based on age (tertiles), obesity, and receiving statins and the risk of type 2 diabetes relative to the lowest risk category (first age tertile, not receiving statins, and without obesity) was investigated using logistic regression. The logistic regression analyses were also run separately in the subgroup with a genetic diagnosis of heterozygous familial hypercholesterolaemia to validate our findings.

The probability of type 2 diabetes as a function of age or BMI was estimated using generalised additive linear models using R package mgcv (version 1.8–39), applying a binomial random error distribution and a logit link function, and incorporating a penalised cubic regression spline for the continuous predictor variable. The models were fitted separately for those receiving or not receiving different types of lipid-lowering medication, adjusting for sex (and age in the case of BMI as predictor). In the models with BMI as predictor, a product interaction term was included to capture possible interactions between BMI and treatment group on the chance of type 2 diabetes. All models were visualised using the R visreg package (version 2.7.0). Statistical significance was defined as p<0·05, with analyses conducted using R Studio (version 22.7.0.548) and IBM SPSS (version 28).

	Pooled globally (n=24 784)*		The Americas (n=1955)		Eastern Mediterranean (n=194)		Europe (excluding Netherlands; n=6579)		Netherlands (n=14 266)†		South-East Asia and Western Pacific (n=1785)‡	
	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes
Number of people	1415 (5·7%)	23 369 (94·3%)	166 (8·5%)	1789 (91·5%)	58 (29·9%)	136 (70·1%)	527 (8·0%)	6052 (92·0%)	450 (3·2%)	13 816 (96·8%)	214 (12·0%)	1571 (88·0%)
Sex												
Male	664 (46·9%)	10 731 (45·9%)	59 (35·5%)	744 (41·6%)	28 (48·3%)	77 (56·6%)	261 (49·5%)	2656 (44·0%)	196 (43·6%)	6488 (47·0%)	120 (56·1%)	765 (48·7%)
Female	751 (53·1%)	12 628 (54·1%)	107 (64·5%)	1044 (58·4%)	30 (51·7%)	59 (43·4%)	266 (50·5%)	3387 (56·0%)	254 (56·4%)	7328 (53·0%)	94 (43·9%)	806 (51·3%)
Missing sex data	..	10	..	1	..	..	..	9	..	..	..	..
Age												
Age at registry entry, years	58·90 (12·64)	46·22 (15·93)	57·20 (12·11)	45·09 (15·25)	51·46 (9·25)	40·50 (11·14)	57·92 (12·32)	49·14 (14·92)	62·64 (12·67)	44·98 (16·44)	56·99 (10·8)	47·92 (14·91)
Age at familial hypercholesterolaemia diagnosis, years	55·82 (14·14)	44·25 (16·23)	56·89 (12·21)	44·86 (15·05)	51·36 (9·75)	38·85 (10·80)	49·14 (13·97)	41·67 (16·16)	62·64 (12·67)	44·96 (16·44)	55·11 (11·02)	45·82 (14·55)
Missing age data	198	1814	46	624	6	27	95	1061	..	..	51	102
Index cases	427 (42·9%)	4042 (21·2%)	46 (37·4%)	456 (39·0%)	2 (100·0%)	22 (64·7%)	193 (85·4%)	2013 (74·4%)	17 (3·8%)	462 (3·3%)	169 (86·7%)	1089 (80·5%)
Missing index data	419	4303	43	619	56	102	301	3358	..	..	19	219
BMI												
BMI, kg/m²	28·41 (25·34–32·66)	24·93 (22·41–27·92)	29·43 (25·80–33·72)	25·37 (22·81–28·56)	31·11 (27·28–34·45)	28·60 (25·84–31·92)	29·62 (26·04–33·00)	26·21 (23·36–29·41)	27·78 (25·13–31·56)	24·39 (22·12–27·11)	26·77 (23·66–31·40)	25·03 (22·21–27·92)
Underweight (<18·5 kg/m²)§	6 (<1%)	479 (2·0%)	0	26 (1·5%)	0	1 (<1%)	3 (<1%)	134 (2·2%)	1 (<1%)	259 (1·9%)	2 (<1%)	57 (3·6%)
Healthy weight (18·5–24·9 kg/m²)§	320 (22·6%)	11 327 (48·5%)	33 (19·9%)	779 (43·5%)	8 (13·8%)	25 (18·4%)	92 (17·5%)	2216 (36·6%)	110 (24·4%)	7579 (54·9%)	77 (36·0%)	727 (46·3%)
Overweight (25·0–29·9 kg/m²)§	577 (40·8%)	3361 (14·4%)	76 (45·8%)	312 (17·4%)	34 (58·6%)	56 (41·2%)	251 (47·6%)	1321 (21·8%)	152 (33·8%)	1436 (10·4%)	64 (29·9%)	235 (15·0%)
Obese (>30·0 kg/m²)§	512 (36·2%)	8202 (35·1%)	57 (34·3%)	672 (37·6%)	16 (27·6%)	54 (39·7%)	181 (34·3%)	2381 (39·3%)	187 (41·6%)	4542 (32·9%)	71 (33·2%)	552 (35·2%)
Comorbidities												
Hypertension	832 (60·3%)	4281 (18·6%)	98 (59·0%)	353 (20·0%)	27 (47·4%)	24 (17·4%)	349 (70·8%)	1925 (33·9%)	231 (51·4%)	1572 (11·4%)	127 (59·3%)	403 (25·7%)
Missing hypertension data	36	406	0	21	1	0	34	376	1	7	0	2
Stroke	74 (6·2%)	388 (1·8%)	9 (7·3%)	16 (1·4%)	0	0	27 (6·8%)	117 (2·6%)	28 (6·2%)	228 (1·7%)	10 (4·7%)	27 (1·7%)
Missing stroke data	228	2308	43	619	56	104	129	1585	0	0	0	0
Coronary artery disease	628 (50·0%)	3549 (16·2%)	61 (36·7%)	287 (16·0%)	0	6 (18·8%)	294 (69·5%)	1513 (31·9%)	157 (34·9%)	1435 (10·4%)	116 (54·2%)	308 (19·6%)
Missing coronary artery disease data	160	1408	0	0	56	104	104	1304	0	0	0	0
Premature coronary artery disease	406 (33·9%)	2080 (9·5%)	5 (17·2%)	46 (11·1%)	20 (43·5%)	26 (26·5%)	226 (49·1%)	1113 (22·5%)	65 (14·4%)	640 (4·6%)	90 (42·1%)	255 (16·2%)

(Table 1 continues on next page)

	Pooled globally (n=24 784)*		The Americas (n=1955)		Eastern Mediterranean (n=194)		Europe (excluding Netherlands; n=6579)		Netherlands (n=14 266)†		South-East Asia and Western Pacific (n=1785)‡	
	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes
(Continued from previous page)												
Missing premature coronary artery disease data	216	2521	137	1374	12	38	67	1104	0	0	0	0
Peripheral artery disease	68 (9·6%)	322 (4·6%)	5 (4·2%)	22 (2·0%)	0	0	62 (15·6%)	285 (6·4%)	0	0	1 (<1%)	15 (1·1%)
Missing peripheral artery disease data	708	16 413	46	664	56	104	129	1592	450	13 816	27	232
Lipids												
LDL cholesterol, mmol/L	4·53 (2·02)	4·68 (1·80)	5·78 (2·20)	6·01 (1·99)	6·08 (1·64)	6·36 (1·96)	4·90 (2·12)	5·10 (2·09)	3·11 (1·09)	4·20 (1·39)	4·86 (1·57)	4·80 (1·68)
Missing LDL cholesterol data	212	5653	41	373	4	11	49	718	112	4501	6	45
HDL cholesterol, mmol/L	1·11 (0·91–1·34)	1·24 (1·01–1·50)	1·06 (0·88–1·22)	1·19 (1·01–1·45)	1·03 (0·78–1·27)	1·11 (0·93–1·29)	1·16 (0·96–1·42)	1·37 (1·14–1·66)	1·01 (0·80–1·24)	1·16 (0·93–1·42)	1·14 (0·98–1·37)	1·32 (1·11–1·60)
Missing HDL cholesterol data	216	5745	40	393	4	19	55	799	109	4470	8	59
Total cholesterol, mmol/L	6·08 (4·76–7·99)	6·31 (5·20–7·81)	8·09 (6·05–9·67)	8·25 (7·06–9·60)	7·97 (6·52–9·28)	8·38 (6·98–9·80)	6·98 (5·28–8·53)	7·24 (5·51–8·69)	4·89 (4·14–5·61)	5·79 (5·02–6·80)	6·21 (4·89–7·50)	6·70 (5·40–7·73)
Missing cholesterol data	185	5246	39	344	4	11	30	537	107	4296	5	53
Triglycerides, mmol/L	1·80 (1·24–2·60)	1·22 (0·84–1·80)	1·77 (1·29–2·77)	1·40 (0·97–2·00)	1·96 (1·52–2·59)	1·56 (1·10–2·29)	1·92 (1·30–2·74)	1·30 (0·90–1·90)	1·54 (1·07–2·39)	1·14 (0·77–1·69)	1·80 (1·30–2·50)	1·40 (0·98–1·90)
Missing triglycerides data	228	5787	41	384	4	18	70	842	108	4482	5	56
Medication												
Use of lipid-lowering medication	1146 (86·4%)	15 330 (67·8%)	141 (86·0%)	1195 (68·3%)	54 (93·1%)	105 (77·2%)	427 (83·9%)	4327 (73·7%)	379 (84·2%)	8840 (64·0%)	145 (100·0%)	858 (83·3%)
Missing lipid-lowering medication data	89	762	2	39	0	0	18	182	0	0	69	541
Statins (with or without other lipid-lowering medication)	1081 (82·3%)	12 334 (54·8%)	133 (83·6%)	1137 (66·5%)	53 (91·4%)	104 (76·5%)	405 (80·5%)	4027 (69·3%)	350 (77·8%)	6217 (45·0%)	140 (97·2%)	844 (82·0%)
Non-statin lipid-lowering medication	53 (4·0%)	2901 (12·9%)	3 (1·9%)	19 (1·1%)	1 (1·7%)	1 (<1%)	16 (3·2%)	245 (4·2%)	29 (6·4%)	2623 (19·0%)	4 (2·8%)	13 (1·3%)
Missing statin data	12	95	5	39	0	0	6	55	0	0	1	1
Smoking status												
Current smoker	346 (26·0%)	6535 (28·6%)	24 (14·5%)	334 (18·9%)	12 (27·3%)	30 (23·4%)	115 (22·8%)	1211 (20·6%)	162 (36·4%)	4731 (34·5%)	33 (19·1%)	229 (17·0%)
Missing smoking status data	84	557	1	26	14	8	23	187	5	115	41	221

Data are n, n (%), median (IQR), or mean (SD). All variables were significantly different (p<0·0001) in people with versus without diabetes globally; no formal comparisons were made for individual regions since these data are mainly descriptive. *Africa is only included in the pooled category due to a sample size (n=5). †The Netherlands was reported as a separate category to Europe due to a proportionately large sample size. ‡South-East Asia (n=143) was combined with Western Pacific (n=1642) due to small sample sizes §WHO BMI categories.

Table 1: **Characteristics of participants with heterozygous familial hypercholesterolaemia and with or without type 2 diabetes stratified by WHO regions**

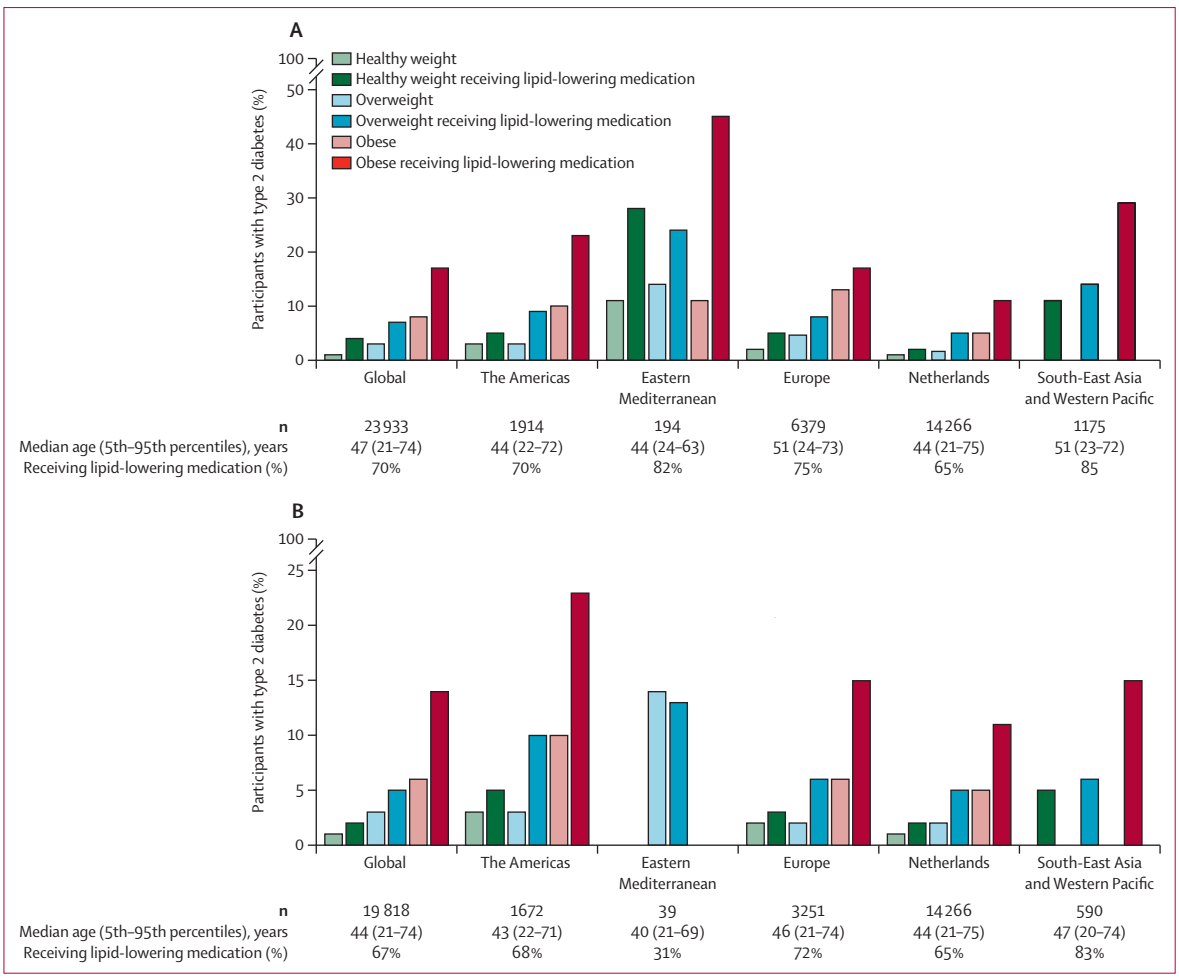

Figure 1: **Prevalence of type 2 diabetes at registry entry in the whole cohort (A) and those with a genetic diagnosis of familial hypercholesterolaemia (B)**
Stratified according to WHO BMI categories (healthy weight 18·5–24·9 kg/m², overweight 25·0–29·9 kg/m², and obese ≥30·0 kg/m²) and use of lipid-lowering medication. Underweight (BMI <18·5 kg/m²) was combined with the healthy weight category due to a small sample size (n=485). Africa (all clinically diagnosed) is only included in the global prevalence due to small sample size (n=5). Globally, in the whole population and genetically diagnosed cohort, the prevalence of diabetes was significantly (p<0·0001) higher across BMI categories, and within each BMI category, in those receiving versus not receiving lipid-lowering medication.

Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Among 46 683 adults with individual-level data in the FHSC registry, 24784 with heterozygous familial hypercholesterolaemia were included in the analysis from 44 countries (appendix p 19). Of these, 19 818 (80%) had a genetically confirmed diagnosis of heterozygous familial hypercholesterolaemia. The whole cohort had a mean age of 46·95 years (SD 16·03), and of those, 13 379 (54·0%) were females and 11 405 (46·0%) were males. In the genetically diagnosed cohort, the mean age was 45·71 (SD 16·45), including 10 754 (54·3%) females and 9064 (45·7%) males.

Table 1 shows the population characteristics in individuals with and without type 2 diabetes pooled globally and by region. Type 2 diabetes prevalence in the total population was 5·7% (1415 of 24784). This low prevalence was mainly driven by the Netherlands, which contributed 14 266 patients (58·0%) with type 2 diabetes prevalence of 3·2% (450 of 14 266). Higher prevalence of type 2 diabetes was observed in the Eastern Mediterranean (58 [29·9%] of 194), South-East Asia and Western Pacific (214 [12·0%] of 1785), and the Americas (166 [8·5%] of 1955) than in Europe (excluding the Netherlands; 527 [8·0%] of 6579). The genetically diagnosed cohort had a lower prevalence of diabetes (817 [4·1%] of 19 818) than the whole cohort, but diabetes prevalence in all regions remained higher than in the Netherlands (appendix p 21).

Globally and in all WHO regions, those with type 2 diabetes were older and were diagnosed with heterozygous familial hypercholesterolaemia at an older age than those without diabetes (table 1). In individuals with type 2 diabetes, the median BMI was 3·5 kg/m² higher than in those without diabetes (28·41 kg/m² [25·34–32·66]

vs 24·93 kg/m² [22·41–27·92]). Combined prevalence of overweight and obesity was higher in those with type 2 diabetes (1089 [77·0%] of 1415; 577 [40·8%] with overweight and 512 [36·2%] with obesity) than in those without type 2 diabetes (11 563 [49·5%] of 23 369; 3361 [14·4%] with overweight and 8202 [35·1%] with obesity). Those with type 2 diabetes also had more frequent comorbidities, including hypertension, coronary artery disease, peripheral artery disease, and a history of stroke than those without type 2 diabetes. Globally, a greater proportion of individuals with type 2 diabetes were receiving lipid-lowering medication (1146 [86·4%] of 1326) than those without (15 330 [67·8%] of 22 607) and a similar pattern was seen across WHO regions. Mean LDL cholesterol in individuals with type 2 diabetes (4·53 mmol/L [SD 2·02]) was 0·15 mmol/L lower than in those without type 2 diabetes (4·68 mmol/L [1·80]).

Overall and by WHO region, the prevalence of type 2 diabetes at registry entry was higher across BMI categories and in any given BMI category, the prevalence was higher in those receiving than in those not receiving lipid-lowering medication (figure 1A). A similar pattern, but with lower type 2 diabetes prevalence, was observed in the genetically diagnosed cohort (figure 1B). Advancing age, a higher BMI category, and use of lipid-lowering medication were independently associated with a higher risk of type 2 diabetes in the whole cohort (table 2). Compared with individuals at a healthy weight, the risk of type 2 diabetes was higher in people with overweight (OR 1·67 [95% CI 1·44–1·93]; p<0·0001) and those with obesity (OR 4·78 [4·14–5·53]; p<0·0001), after adjusting for age, sex, and lipid-lowering medication in model one. After further adjustment for LDL cholesterol in model two, the strong association of body weight with type 2 diabetes remained. Similar results were seen in the genetically diagnosed cohort (table 2). Findings from the original non-imputed dataset were also similar (appendix p 23). The findings were confirmed in a sensitivity analysis of a subset of the whole cohort in which investigators confirmed the type of diabetes (appendix p 24).

Figure 2 shows the probability of having type 2 diabetes as a function of BMI in the whole cohort on a continuous scale for those receiving different types of lipid-lowering medication, adjusted for age and sex. The probability of type 2 diabetes increased with higher BMI, with a steep increase at BMI of more than 30·0 kg/m², with a non-significant trend for higher type 2 diabetes probability in those receiving lipid-lowering medication (figure 2A). When the population was split according to the type of lipid-lowering medication, those receiving statins had a higher risk of type 2 diabetes than those who were not receiving lipid-lowering medication or were receiving non-statin lipid-lowering medication (figure 2B). Among those receiving statins, the group receiving highest potency statins had a greater risk of type 2 diabetes than those receiving other statin regimens (appendix p 28). There was no interaction between BMI and treatment on the probability of type 2 diabetes ($p_{interaction}$≥0·70 in all models).

In subsequent analysis, a BMI cutoff of 30·0 kg/m² (obese category) was used for stratification. Compared with people who were not receiving statins, those receiving statins were older at heterozygous familial hypercholesterolaemia diagnosis and at registry entry, with a higher median BMI and a higher type 2 diabetes prevalence (appendix p 25). Since age might be indicative of the duration of exposure to adverse dietary and lifestyle factors related to type 2 diabetes, we investigated the risk of type 2 diabetes with advancing age, stratified by obesity and statins and adjusted for sex. We pooled data on those not receiving lipid-lowering medication and those receiving non-statin lipid-lowering medication because exploratory analysis showed that the trajectories of these two groups were similar (appendix p 29). Figure 3A shows that the rise in type 2 diabetes with age followed different trajectories depending on the presence or absence of obesity and receiving statins, with the

	Odds ratio (95% CI) in model one	p value	Odds ratio (95% CI) in model two*	p value
Whole cohort (n=24 784)				
Age (per year increase)	1·05 (1·05–1·05)	<0·0001	1·05 (1·05–1·05)	<0·0001
Sex (female *vs* male)	0·81 (0·72–0·90)	0·0010	0·80 (0·71–0·90)	0·0011
With overweight (BMI 25·0–29·9 kg/m²)†	1·67 (1·44–1·93)	<0·0001	1·67 (1·43–1·94)	<0·0001
With obesity (BMI ≥30·0 kg/m²)†	4·78 (4·14–5·53)	<0·0001	4·75 (4·11–5·49)	<0·0001
Lipid-lowering medication (yes *vs* no)	1·91 (1·62–2·26)	<0·0001	1·95 (1·65–2·30)	<0·0001
Genetically diagnosed cohort (n=19 818)				
Age (per year increase)	1·05 (1·05–1·06)	<0·0001	1·05 (1·05–1·06)	<0·0001
Sex (female *vs* male)	0·95 (0·82–1·10)	0·54	0·97 (0·84–1·13)	0·65
With overweight (BMI 25·0–29·9 kg/m²)†	1·90 (1·57–2·30)	<0·0001	1·91 (1·58–2·30)	<0·0001
With obesity (BMI ≥30·0 kg/m²)†	5·44 (4·50–6·58)	<0·0001	5·52 (4·56–6·68)	<0·0001
Lipid-lowering medication (yes *vs* no)	1·79 (1·46–2·20)	<0·0001	1·68 (1·37–2·07)	<0·0001

Both models simultaneously have all variables as predictors. *Model two is additionally adjusted for LDL cholesterol. †WHO BMI categories, each compared with healthy weight (BMI 18·5–24·9 kg/m²). Underweight (BMI <18·5 kg/m²) was combined with the healthy weight category due to a small sample size.

Table 2: **Independent factors associated with type 2 diabetes at registry entry**

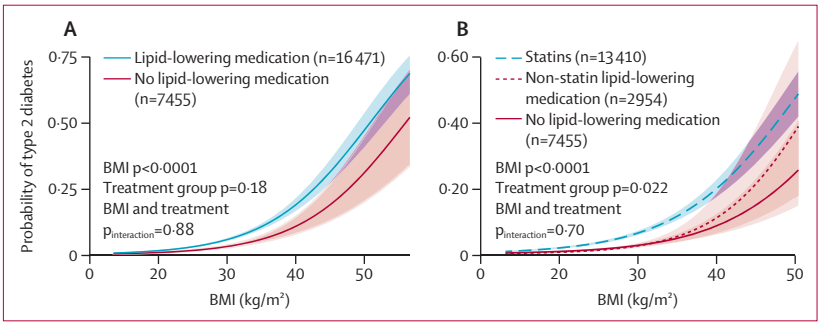

Figure 2: **Predicted probability of type 2 diabetes at registry entry as a function of BMI**
Shaded areas represent 95% CI. Adjusted for age and sex in the pooled study cohort. (A) Participants receiving or not receiving lipid-lowering medication. (B) Those not receiving lipid-lowering medication, receiving non-statin lipid-lowering medication, or receiving statins.

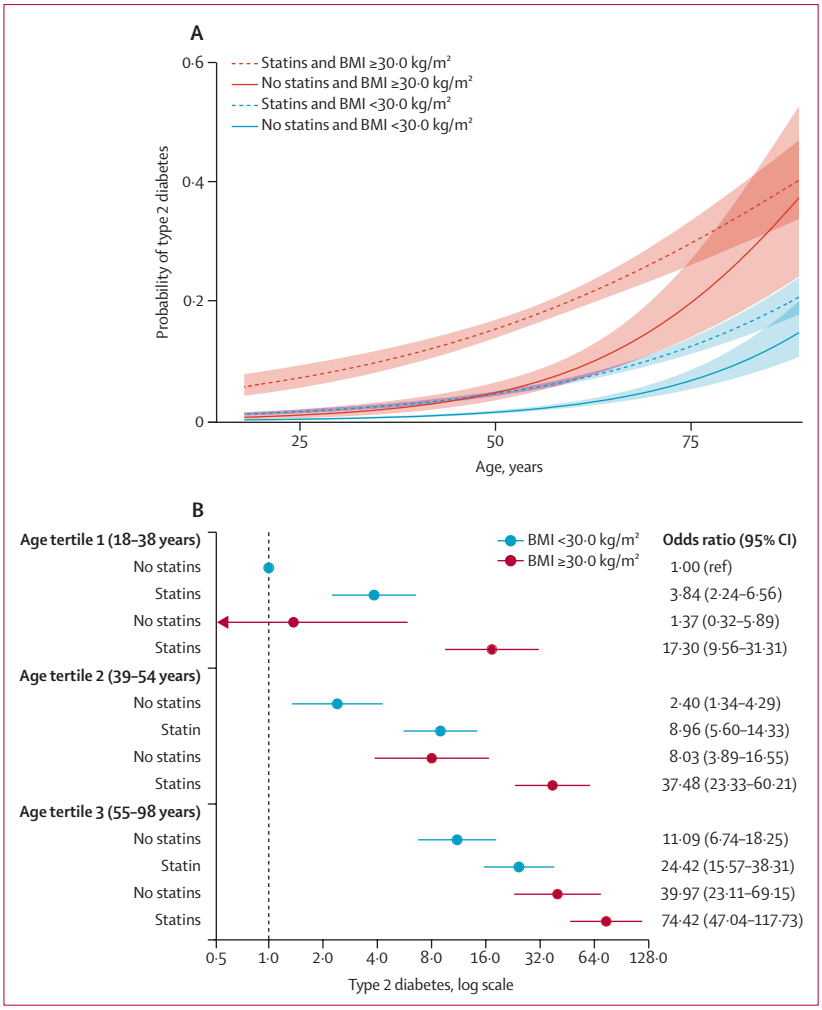

Figure 3: **Type 2 diabetes as a function of age, statin treatment, and obesity**
(A) Predicted probability of having type 2 diabetes in the whole population as a function of age, stratified by BMI category and use of statins, adjusted for sex (n=23 234 for four groups). Shaded areas represent 95% CIs. (B) Odds ratio with 95% CIs of having type 2 diabetes by age tertile, BMI category, and use of statins compared with patients in the lowest age tertile with BMI of less than 30 kg/m² and not receiving statins (reference category), adjusted for sex (n=23 234 for 12 groups). The no statins groups include patients who were not receiving lipid-lowering medication and those exclusively receiving non-statin lipid-lowering medication.

highest risk in those with obesity and who were receiving statins.

When the population was split into 12 risk categories, the probability of type 2 diabetes was 74 times higher in people in the highest risk category (upper age tertile 55–98 years, with obesity, and receiving statins; OR 74·42 [95% CI 47·04–117·73]) than in those in the lowest risk category (reference group lowest age tertile 18–38 years, without obesity, and not receiving statins; OR 1·00; figure 3B). Those who did not have obesity, even if they were in the upper age tertile and receiving statins, had lower risk of type 2 diabetes (OR 24·42 [15·57–38·31]). The corresponding ORs in the genetically diagnosed cohort were OR 65·04 (40·67–104·02) for those with obesity in the highest risk category and OR 20·07 (12·73–31·65) for those without obesity (appendix p 30).

Discussion

Heterozygous familial hypercholesterolaemia was proposed to possibly be protective against type 2 diabetes based on three cohorts from the Netherlands,[4] Spain,[5] and Canada[6] with early detection and management of familial hypercholesterolaemia. In our study on 24 784 adults with heterozygous familial hypercholesterolaemia from 44 countries, the prevalence of type 2 diabetes was 5·7% overall and varied greatly, with the highest regional prevalence in South-East Asia and Western Pacific and Eastern Mediterranean regions and lowest in Europe. The age-standardised prevalence of diabetes in adults globally was 6·1% in 2021, according to a Global Burden of Disease study.[12] The International Diabetes Federation estimates that the global prevalence of diagnosed diabetes was 4·6% in 2019 (9·3% living with diabetes and half of those were undiagnosed).[13] These percentages are broadly similar to the prevalence of global type 2 diabetes observed in our study (5·7% in the whole cohort and 4·1% in the genetically diagnosed cohort). Considering that our population has an overrepresentation of Europe and an underrepresentation of other world regions, in which type 2 diabetes prevalence is higher (such as the Middle East),[13] our data suggests that globally, people with heterozygous familial hypercholesterolaemia do not appear to be protected against type 2 diabetes.

Previous studies reported low prevalences of type 2 diabetes in Dutch[4] and Spanish[5] cohorts (1·75% and 2·30%) with genetic confirmation of heterozygous familial hypercholesterolaemia compared with unaffected family members (2·93% and 3·60%). Heterozygous familial hypercholesterolaemia was hypothesised to reduce susceptibility to type 2 diabetes owing to the reduction in fully functioning LDL receptors required for pancreatic cellular uptake of cholesterol affecting β-cell function.[14] Our findings confirmed that the overall risk of type 2 diabetes was higher with obesity, use of statins, and advancing age (even in the genetically diagnosed cohort) suggesting that those with heterozygous familial hypercholesterolaemia are likely to be prone to the same risk factors of type 2 diabetes as the general population.

Individuals with heterozygous familial hypercholesterolaemia, especially those who are not yet diagnosed, are likely to be at risk of adopting the same adverse lifestyle factors as the general population and be at a similar risk of obesity. This theory is supported by our earlier observations suggesting that as the age of heterozygous familial hypercholesterolaemia diagnosis increases, the likelihood of obesity, hypertension, and diabetes also increases.[8] Hence, studies diagnosing this condition earlier would most likely offer lifestyle advice sooner, meaning that favourable lifestyles were more likely to be adopted earlier in life. For example, data from the Netherlands resulted from a nationwide publicly funded cascade screening programme for familial hypercholesterolaemia that lasted for 20 years[4]

and identified many non-index cases. We previously reported that non-index cases were younger, with lower LDL cholesterol, and lower prevalence of atherosclerotic cardiovascular disease and its risk factors than index cases.[8] This finding suggests that lifestyle factors could have been addressed early in life in the Netherlands, hence the low prevalence of type 2 diabetes, rather than a true effect of heterozygous familial hypercholesterolaemia protection against type 2 diabetes.

Statins increase the risk of type 2 diabetes in a dose-dependent way in people without heterozygous familial hypercholesterolaemia.[15–17] In our study, the highest potency statins were associated with a higher chance of type 2 diabetes across a range of BMIs compared with other statin regimens; therefore, reduced lipotoxicity from having fewer functioning LDL receptors (the most common abnormality in heterozygous familial hypercholesterolaemia) might not attenuate the increase in type 2 diabetes associated with statin use. However, the SAFEHEART[5] and ATTICA[18] studies reported that statins were not associated with prevalence of type 2 diabetes in Spanish and Greek cohorts with heterozygous familial hypercholesterolaemia. These differences might be partly explained by clinically well managed cohorts[5,18] with a lower prevalence of, and systematic management of, risk factors predisposing to diabetes, fewer participants with prediabetes and differences in duration of treatment. Furthermore, we found a lower chance of type 2 diabetes across ages when those people did not receive statins irrespective of whether alternative lipid-lowering medication was used, further supporting the notion that statins rather than LDL cholesterol lowering might be associated with type 2 diabetes in heterozygous familial hypercholesterolaemia and the general population. However, the reduction in the risk of atherosclerotic cardiovascular disease from cholesterol lowering with statins likely outweighs the risk of type 2 diabetes in the general population.[19] In the 4S trial of simvastatin versus placebo, those with a heterozygous familial hypercholesterolaemia phenotype had greater reductions in the risk of atherosclerotic cardiovascular disease and all-cause mortality with statins for the same amount of LDL cholesterol lowering than those without this phenotype,[20] underscoring the overall benefit of statins in heterozygous familial hypercholesterolaemia. In our study, the risk of type 2 diabetes was higher with obesity than with statin use. Similarly, the ATTICA study[18] reported that BMI and waist circumference were among the greatest predictors of type 2 diabetes in those with heterozygous familial hypercholesterolaemia. Similar to people without familial hypercholesterolaemia, early and sustained diet and lifestyle measures might prevent or delay the risk of type 2 diabetes for those with heterozygous familial hypercholesterolaemia, in whom statins are essential and are the most affordable lipid-lowering medication globally.

Although alternative therapies to statins such as ezetimibe, PCSK9 inhibitors, and bempedoic acid have not been found to increase the risk of new onset diabetes,[21–25] the accessibility and affordability of these newer therapies differs by country and hence, they might not be a viable alternative in low-income countries in which obesity is rapidly increasing. With patients having greater access to online resources, concerns about medication safety are becoming an increasing challenge in routine clinical practice.[26] Our observations underscore that although statins might increase the risk of diabetes, this effect is trivial compared with the risk seen in people who are obese. Since statins are the main treatment for preventing adverse cardiovascular outcomes in heterozygous familial hypercholesterolaemia, our data have a practical importance since reaching early detection of this condition and adoption of favourable sustained lifestyle factors, which are more amenable to change when people are younger, could possibly help to prevent the development of type 2 diabetes in these individuals in later life.

Our study has limitations. First, the cross-sectional design could not confirm causality and temporal relationships since we could not determine whether the exposures occurred before the outcome, particularly because individuals with diabetes were more likely to have been prescribed statins. Second, an incidence–prevalence bias cannot be excluded as individuals with longer duration of type 2 diabetes were more likely to be included in the study and prescribed lipid-lowering medication, which could have inflated the association of lipid-lowering medication with the risk of type 2 diabetes. However, this association appeared to be specific to statins, but not other medication classes, and is in line with prospective data showing dose-dependent increases in diabetes incidence with statin treatment in the general population.[16,17] This increase did not occur with ezetimibe, PCSK9 inhibitors, or bempedoic acid.[22,24,25] Third, if diagnosis and treatment of people with heterozygous familial hypercholesterolaemia improve and are instigated early in life, then we assume that lifestyle-related factors that increase the risk of obesity might become more relevant over the life course of care. The comparison between patients receiving statins and those receiving alternative medications is imbalanced, with the alternative medication group being smaller and consisting of a younger population, which might explain their lower risk of diabetes. However, our results show that those receiving alternative (non-statin) lipid-lowering medication had a lower probability of diabetes than those receiving statins, even after adjusting for younger age.

In logistic regression, we adjusted for potential confounders, but there might have been residual confounding from unmeasured variables and the time-varying confounding effects—eg, of lipids—could not be assessed due to an absence of repeated measurements. To investigate potential interactions between BMI and medication use on the risk of type 2 diabetes we included a product term in the models. This approach, although commonly used in epidemiological research, assesses multiplicative

interaction, whereas an additive interaction might be more relevant from a causal and public health perspective.[27] The number of participants available from the contributing countries were disproportionate, with some missing data where indicated, but the results before and after multiple imputation to account for missing data were similar, suggesting that potential biases from missing data did not influence the results. In cases in which the diabetes type was not reported, we assumed type 2 (ie, the most common type in adults); and sensitivity analysis in those with confirmed type 2 diabetes showed consistent results. Not all cases of heterozygous familial hypercholesterolaemia were genetically confirmed, but 80% were genetically confirmed, and separate analyses in this cohort were similar to primary analysis findings. Finally, we considered whether statin exposure and the risk of type 2 diabetes was a class effect but concluded that this assumption might not be the case as pitavastatin did not adversely affect HbA1c or diabetes development compared with placebo or other statins in a meta-analysis of 15 statin-controlled trials with at least 12 weeks of follow-up.[28]

In conclusion, our cross-sectional analysis using global data and a more heterogenous population of people with familial hypercholesterolaemia than previously investigated, suggests that this condition is not protective against the development of type 2 diabetes. Factors known to be associated with a greater likelihood of type 2 diabetes in the general population, especially obesity, appear to be highly relevant to those with heterozygous familial hypercholesterolaemia. For patients concerned about the benefit–risk profile of statins with respect to LDL cholesterol control versus the risk of diabetes, notably the markedly increased probability of type 2 diabetes associated with obesity overshadowed the potential effect of statins on type 2 diabetes. Since lipid-lowering medication is initiated at the point of diagnosis, reaching an early diagnosis of heterozygous familial hypercholesterolaemia and helping patients to maintain control of lifestyle factors related to obesity might help to avoid the development of type 2 diabetes in those at already substantially elevated risk of atherosclerotic cardiovascular disease.

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AE and ARML contributed to the manuscript equally. AE, ARML, AJVV, and KKR designed the study. All authors contributed to data acquisition and interpretation. AE conducted the statistical analysis. AE, ARML, and KKR wrote the manuscript. All authors provided critical review of the manuscript and approved submission. AE and AJVV have accessed and verified all the data in the study. All authors had final responsibility for the decision to submit for publication. The Imperial College London coordinating centre has full access to all the data in the study.

Declaration of interests

CAA-S reports support from Amgen to their institution. MAb reports support from Amryt for lectures and from Newbridge and Amryt to attend meetings. MAr reports grants to their institution from Novartis, Ionis, Lilly, and Amgen; and honoraria from Viatris, Alfasigma, Sanofi, Amgen, PIAM, Amaryn, Novartis, Ionis, and Ultragenyx. MAv reports consultancy fees from Akcea, Amgen, Amrith, Aurora Biofarma, Daiichi-Sankyo, Menarini, Novartis, Sanofi (Genzyme), and Sobi; and honoraria from Amgen, Amrith, Aurora Biofarma, Daiichi-Sankyo, Menarini, Novartis, Sanofi (Genzyme), and Sobi. FA reports support, consultancy fees, honoraria, and participation on a data safety monitoring or advisory board from Amgen, Amryt, and Novartis. RA reports honoraria from Amgen, Novo Nordisk, Tecnofarma, Saval, Abbott, and PTC-Therapeutics; support to attend meetings from Amgen And PTC-Therapeutics; participation on a data safety monitoring or advisory board for PTC-Therapeutics; and leadership or fiduciary, society, committee or advocacy group for Chilean Atherosclerosis

Working Group. MBa reports participation at speakers bureaus for Amgen, Daiichi-Sankyo, Krka, Polpharma, Novartis, Sanofi-Aventis, Teva, and Zentiva; being a consultant for Adamed, Amgen, Daiichi-Sankyo, Esperion, New Amsterdam, Novartis, and Sanofi-Aventis; and grants from Amgen, Daiichi-Sankyo, Novartis, and Sanofi. CJB reports funding to the Austrian Familial Hypercholesterolaemia Registry from Amgen, Daiichi-Sankyo, Sanofi, and Novartis; consultancy fees from Novartis And Daiichi-Sankyo; and honoraria from Amgen and Novartis. MBo reports a grant to their institution from the Portuguese Science and Technology Foundation and Portuguese Cardiology Society. JB reports grants from AstraZeneca and honoraria from Amgen. LRB reports consultancy fees from Ultragenyx and Amryt; and honoraria from Amgen, HLS Therapeutics, and Novartis. ALC reports grants from Amryt, Menarini, and Ultragenyx; and honoraria from Amarin, Amgen, Amryt, AstraZeneca, Daiichi-Sankyo, Esperion, Ionis Pharmaceutical, Medscape, Menarini, Merck, Novartis, Novo Nordisk, PeerVoice, Pfizer, Recordati Regeneron, Sandoz, Sanofi, The Corpus, Ultragenyx, and Viatris. PC reports grants to FASTA University from Amgen; and consultancy fees and other honoraria from Amgen and Novartis. DC reports consultancy fees, including data safety monitoring, from Ultragenyx, Organon, and Novartis; honoraria from Bial, Alexion (Synageva), Daiichi-Sankyo, Amgen, Novartis, Organon, and Servier; support for attending meetings from Servier, Daiichi-Sankyo, and Medinfar; is the vice president of the Portuguese Atherosclerosis Society; and is a board member and ex-deputy director health of the Portuguese Society of Internal Medicine. 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UG reports grants from the Slovenian Research Agency and UMC Ljubljana Grant; honoraria from AstraZeneca and Novartis; and participation on a data safety monitoring board for Familial Hypercholesterolaemia Europe Foundation. KBH reports consultancy fees and other honoraria from Sanofi and participation in a scientific advisory board for Familial Hypercholesterolaemia Europe Foundation. GKH reports being a part-time employee of Novo Nordisk. MK reports honoraria for lectures and consultancy from Abbott, Abdi Ibrahim, Amryt, Novo Nordisk, and Tr-Pharma; funding from Amryt; participation in clinical trials with payments to their institution from Amgen, Ionis, Lib Therapeutics, Novo Nordisk, Sanofi, and Medpace; and participation in an unpaid advocacy group for Familial Hypercholesterolaemia-Türkiye and Familial Hypercholesterolaemia Europe Foundation. WK reports grants to their institution from Health Systems Research Institute; payments from Medical Council of Thailand, Royal College of Physicians of Thailand, Chulalongkorn University, Endocrine Society of Thailand, and Amgen; other honoraria from Amgen, Novartis, Boehringer, AstraZeneca, Abbot, and Thai Meiji; support to attend meetings from Amgen; and participation on an advisory board for Daiichi-Sankyo, Amgen, Kowa (Biopharm), Thai Meiji, Novartis, and Abbott. KL reports honoraria from Novartis, Novo Nordisk, AstraZeneca, and Boehringer. GL reports grants to their institution from Latvian Science Council (lzp-2020/1–0151), Latvian National Research Program Biomedicine for Public Health 2014–2017, the Ministry of Education and Science of the Republic of Latvia, and VPP-EM-BIOMEDICĪNA-2022/1–001 (*State research project in the field of biomedicine, medical technologies and pharmacy*); consultancy fees from Amgen, Novartis, Novo Nordisk, Boehringer Ingelheim, and Bayer; other honoraria from Pfizer, AstraZeneca, Servier, Sanofi, Novartis, Swixx BioPharma, Novo Nordisk, Boehringer Ingelheim, Bayer, Siemens Laboratories, Abbott Laboratories, and Roche Laboratories; support for attending meetings from Amgen, Bayer, Servier, and Sanofi; participation on data safety monitoring board for Amgen, Novartis, Novo Nordisk, Boehringer Ingelheim, and Bayer; and is a member of the certification council at the Latvian Medical Association Board, Latvian Society of Cardiology Board, and the Baltic Atherosclerosis Society. 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BGN reports consultancy fees from AstraZeneca, Sanofi, Regeneron, Ionis, Amgen, Kowa, Denka, Amarin, Novartis, Novo Nordisk, Esperion, Silence Therapeutics, and Ultragenyx; other honoraria from Sanofi, Kowa, Denka, Amarin, Novartis, Novo Nordisk, Abbott, and Mankind; board participation for Ionis, Kowa, and Novartis; and research collaboration with AstraZeneca. AGP is a board member of the Cyprus Atherosclerosis Society. FJR reports grants and personal fees from Amgen, Regeneron Pharmaceuticals, Novartis, and Lib Therapeutics. KKR reports grants to their institution from Amgen, Sanofi, Regeneron, Daiichi-Sankyo, and Ultragenyx; consultancy fees for serving as a member of the steering committee or executive committee of clinical trials and roles as principal investigator and national lead investigator and for attending advisory boards, providing advice on data interpretation, and future lines of research from Novartis, Daiichi-Sankyo, Kowa, Esperion, Novo Nordisk, MSD, Lilly, Silence Therapeutics, Az, New Amsterdam Pharma, Bayer, Beren Therapeutics, Cleerly, EmendoBio, Scribe, Crispr, Vaxxinity, Amarin, Regeneron, Ultragenyx, Cargene, and Resverlogix; lecture fees from Novartis, Bi, Az, Novo Nordisk, Viatris, Amarin, Biologix Pharma, Sanofi, Amgen, Esperion, Daiichi-Sankyo, Macleod Pharma for symposia at international meetings; holding stock options from New Amsterdam Pharma and Pemi31; and serving as a president for the European Atherosclerosis Society. ŽR reports grants from Sanofi Aventis and Novartis. RDS reports grants from Kowa, Amgen, Sanofi, Regeneron, Novartis, and Esperion; consultancy fees from Amgen, Novartis, Novo Nordisk, Amryt, Pfizer, Hypera, and Sanofi; and support to attend meetings from Novo Nordisk and Daiichi-Sankyo. HSc reports grants from AstraZeneca and consultancy fees from Amgen, AstraZeneca, Bayer Vital, Bristol Myers Squibb, MSD, Novartis, Servier, Sanofi-Aventis, Boehringer Ingelheim, Daiichi-Sankyo, and SYNLAB. CATS reports grants to their institution from Pfizer, Amgen, MSD, Sanofi Aventis, Daiichi-Sankyo, and Regeneron. MT reports grants, consultancy fees, other honoraria, support to attend meetings, and participation on an advisory board for Novartis. AJV-V reports grants to their institution from Pfizer, Amgen, MSD, Sanofi-Aventis, Daiichi-Sankyo, and Regeneron; consultancy fees from Bayer and Regeneron; other honoraria from Ferrer, European Atherosclerosis Society, and USA National Lipid Association; and support for attending meetings from the European Atherosclerosis Society, USA National Lipid Association, and Spanish Atherosclerosis Society. BV reports consultancy fees from Novartis, Amgen, Sanofi, and Zentiva; support to attend meetings from Zentiva; participates on a board for Novartis and Zentiva; and is the president of the Slovak Association of Atherosclerosis. LW reports grants from the National Key Research and Development Program of China and National Natural Science Foundation of China. GFW reports grants to their institution from Arrowhead Pharma, Amgen, Novartis, and Silence Therapeutics; consultancy fees from Amgen, Novartis, Sanofi, and Esperion; other honoraria from Amgen, Novartis, Sanofi, and Esperion; and support for attending meetings from Amgen, Novartis, Sanofi, and Esperion. ES reports consultancy fees to their institution from Amgen, Sanofi, Novo-Nordisk, Ionis, Merck, Novartis, and AstraZeneca. All other authors declare no competing interests.

Data sharing

Data collected in the FHSC registry cannot be shared with third parties owing to clauses in data sharing agreements with data suppliers. Ownership of the data shared with the FHSC registry remains the property of the respective data suppliers.

Acknowledgments

This study was funded by investigator-initiated research grants to Imperial College London (London, UK) from Pfizer (number 16157823), Amgen, MSD, Sanofi-Aventis, Daiichi-Sankyo, and Regeneron. KID acknowledges support for a PhD Studentship from the National Institute for Health and Care Research (NIHR) Applied Research Collaboration Northwest London. KKR acknowledges support from the NIHR Applied Research Collaboration Northwest London and Imperial NIHR Biomedical Research Centre. The views expressed in this Article are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. AJVV acknowledges support from the Programme "Beatriz Galindo" from the Ministry of Universities, Spain, and University of Seville, Spain. The Austrian Familiar Hypercholesterolemia Registry has been supported by funds form the Austrian Heart Foundation and the Tyrolean Regional Government. The work by ALC is supported in part by the grant Ricerca Corrente from the Ministry of Health to IRCCS MultiMedica. The Austrian Familiar Hypercholesterolemia Registry, which has contributed to the FHSC Registry, has been supported by funds form the Austrian Heart Foundation and the Tyrolean Regional Government.

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