Atherosclerosis 415 (2026) 120717

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Traditional cardiovascular risk factors and their association with atherosclerotic cardiovascular disease in homozygous familial hypercholesterolemia: A cross-sectional analysis from the HICC registry

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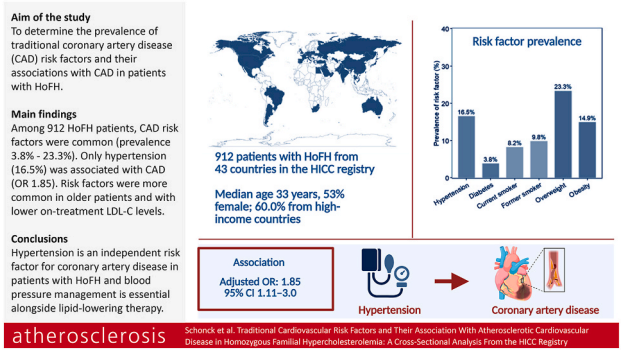
HIGHLIGHTS

- Hypertension is independently associated with coronary artery disease in homozygous familial hypercholesterolemia.
- Diabetes, smoking, and obesity showed no statistically significant association with coronary artery disease.
- Cardiovascular risk factors are more prevalent in older patients and in high-income countries.
- Identification and management of hypertension remain important alongside intensive LDL-C lowering.

GRAPHICAL ABSTRACT



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https://doi.org/10.1016/j.atherosclerosis.2026.120717
Received 30 December 2025; Received in revised form 4 March 2026; Accepted 19 March 2026
Available online 23 March 2026

ARTICLE INFO

Keywords:
Homozygous familial hypercholesterolemia
Cardiovascular disease
Hypertension
Diabetes
Obesity
Smoking

ABSTRACT

Background and aims: As survival improves in patients with homozygous familial hypercholesterolemia (HoFH), exposure to traditional cardiovascular risk factors may increasingly influence outcomes. This study aimed to determine the prevalence of traditional coronary artery disease (CAD) risk factors—hypertension, diabetes, smoking, and obesity—and their associations with CAD in HoFH.

Methods: We performed a cross-sectional analysis of patients enrolled in the HoFH International Clinical Collaborators (HICC) registry (NCT04815005) between February 2016 and December 2024. Logistic regression was used to estimate the association between risk factors and CAD in risk factor propensity score–matched subgroups. Analyses were stratified by sex, on-treatment LDL-C tertiles, and country-income status.

Results: Among 912 patients with HoFH (53.3% female; median age 33.0 years), the prevalence of hypertension was 16.5%, diabetes 3.8%, smoking 8.2%, overweight 25.4%, and obesity 17.6%. Cardiovascular risk factors were more frequent in older patients (e.g., hypertension: 25.7% $\geq$ 30 years vs. 4.3% $<$ 30 years; $p < 0.001$), in those from high-income countries (17.8% vs. 14.9%; $p = 0.011$), and in those achieving lower LDL-C levels (24.1% in the lowest vs. 14.6% in the highest LDL-C tertile; $p = 0.004$). After propensity score matching, hypertension was significantly associated with CAD (OR 1.85; 95%CI 1.11–3.08, $p = 0.02$), while diabetes, smoking, and obesity were not associated.

Conclusions: Despite the dominant role of cumulative LDL-C burden in the development of CAD, our findings indicate an association between hypertension and CAD in HoFH. Although causal inference is limited by the cross-sectional design, these results highlight the importance of proactive identification and management of hypertension in HoFH alongside intensive lipid-lowering therapy.

1. Introduction

Homozygous (bi-allelic) familial hypercholesterolemia (HoFH) is a rare, heritable disease characterized by extremely elevated low-density lipoprotein cholesterol (LDL-C) levels and premature coronary artery disease (CAD) [1,2]. The onset and severity of CAD in HoFH patients varies considerably [3] and is highly dependent on access to lipid lowering therapies (LLT) and achieved lipid control [2]. While care for HoFH has improved substantially, leading to increased life expectancy, other traditional cardiovascular risk factors, such as hypertension, diabetes and obesity, are likely to have an increasing impact in this patient group, especially given their rising global incidence [4]. Emerging data have confirmed that these established risk factors contribute to the increased risk of CAD in patients with heterozygous (mono-allelic) FH (HeFH) [5]; yet the prevalence of these risk factors (i.e., hypertension, diabetes, smoking and obesity) and their association with CAD in HoFH have not been studied at scale. The aim of the current study was to address this gap using the HoFH International Clinical Collaborators (HICC) registry containing more than 900 patients; the largest international HoFH cohort to date.

2. Patients and methods

2.1. Participating centres and patient selection

The HoFH International Clinical Collaborators (HICC, NCT04815005) is a global consortium of clinicians and researchers involved in the care of patients with HoFH [2]. Patients were eligible for inclusion in the HICC registry if diagnosed with HoFH either clinically, genetically, or both by their attending physician. A clinical diagnosis was defined as an untreated LDL-C >10 mmol/L, cutaneous or tendon xanthomas before age 10, and/or elevated LDL-C in both parents (or one in digenic form) [1]. Genetic confirmation involved identifying bi-allelic familial hypercholesterolemia variants (such as homozygous, compound heterozygous, or double heterozygous variants in the *LDLR, APOB, PCSK9* genes), according to local genetic analysis. Over 43 countries contributed to the patients in HICC currently selected for analyses (Supplementary Table S1).

2.2. Data collection

Patients with HoFH who were alive during or after 2010 were eligible for data entry, which occurred between February 2016 and August 2024. The present study has a cross-sectional design involving the data that was collected at the time of entry into the registry and included demographics, lipid levels, lipid-lowering treatment, the prevalence of traditional cardiovascular risk factors. Despite, retrospective collection of data on CAD and ASCVD events no prospective follow-up was performed and the data was cross-sectionally analysed. Detailed description of the data collection methods was outlined in a previous publication [2].

2.3. Variables and subgroup definitions

Physician-reported data on cardiovascular risk factors (i.e. hypertension, diabetes, smoking and overweight/obesity) present at study entry were analysed. These risk factors were classified into categories. Hypertension, diabetes mellitus, and smoking were classified as yes/no. For smoking “no” indicated never-smoker or former smoker and “yes” indicated current smoker. Weight categories were classified according to World Health Organization (WHO) cutoffs: obese (body mass index (BMI) $\geq$30 kg/m^2), overweight (BMI 25–<30 kg/m2), normal weight (BMI 18.5–<25 kg/m2), and underweight (BMI <18.5 kg/m2) [6]. For children and adolescents, BMI z-scores were calculated based on age, sex, height, and weight using WHO growth reference standards [7] as implemented in the R statistical package ‘anthroplus’[8]. Weight status was defined as follows: obese (>+2 standard deviations (SD)), overweight (>+1 SD and ≤+2 SD), normal weight (between −2 SD and +1 SD), and underweight (<−2 SD). In instances where only BMI was available (without accompanying height or weight data), weight classification was determined using WHO BMI-for-age reference tables, stratified by sex [9,10].

CAD was defined as a composite of cardiovascular death, myocardial infarction (MI), percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). ASCVD included CAD and ischemic stroke, carotid endarterectomy, and peripheral artery disease.

For the comparison between high-income and non-high-income regions of the world, countries were categorized according to the 2024 World Bank definition of income categories: high income, upper-middle income, lower-middle income, and low-income (Supplementary Table S1) [11]. The upper-middle income, lower-middle income, and low-income countries were combined into a single "non-high-income" category, as used previously [12].

2.4. Statistical analysis

Descriptive statistics were presented as mean ± standard deviation (SD) for normally distributed variables and as median with interquartile range [IQR] for non-normally distributed data. Appropriate statistical tests were used to compare these descriptive data among groups (i.e., *t*-test, Mann-Witney U, or chi-square test).

Missing data in the variables of interest, was addressed by applying multiple imputation using the mice (Multivariate Imputation by Chained Equations) package. Only records with complete information on age at entry, sex, diagnostic age, and country were retained for imputation. Missing values (Supplementary Table S2) in the dataset were imputed using predictive mean matching for continuous variables and logistic regression for binary categorical variables, based on a manually pre-specified predictor matrix based on domain knowledge (Supplementary Table S3). Ten multiple imputed datasets were generated. The convergence of the imputation process was assessed by examining the logged events and diagnostic plots. The final, imputed datasets included the variables age at entry, sex, age at diagnosis, lipid levels (e.g., LDL-C), lipid lowering therapy use, presence of traditional risk factors (hypertension, diabetes mellitus, smoking status, BMI), and country income status.

To address survivor and reporting bias—particularly relevant in HoFH, where outcomes are strongly influenced by the severity of hypercholesterolemia and access to lipid-lowering therapies—risk factor propensity score matching was performed to create two comparable groups with and without presence of risk factor of interest. The propensity score was estimated using a predefined set of covariates (age at diagnosis, age at registry entry, sex, and lowest on-treatment LDL-cholesterol), selected based on their established relationship with both the likelihood of developing traditional risk factors and the probability of having coronary artery disease (CAD).

Propensity score matching was conducted using the *MatchThem* R package across 10 multiply imputed datasets. Nearest-neighbour matching without replacement was performed within each imputed dataset using the "within" imputation approach, applying a caliper of 0.4 standard deviations of the logit of the propensity score to improve covariate balance and avoid poor matches. A 1:1 matching ratio was used.

Covariate balance before and after matching was assessed using standardized mean differences (SMDs) and Kolmogorov–Smirnov tests, with adequate balance defined as an absolute SMD <0.1. Propensity score overlap between exposed and unexposed groups was visually inspected. Overlap plots and SMD tables are provided in the Supplementary Table S4 and Supplementary Figure 1. All regression analyses presented in the manuscript were performed in the propensity score–matched datasets. In addition to propensity score–matched analyses, we performed multivariable logistic regression in the overall imputed cohort as a complementary analysis, to assess the consistency of associations (Supplementary Table S5).

The prevalences of cardiovascular risk factors were assessed in the overall cohort and stratified by sex, age category, lowest on-treatment LDL-C tertile, and country income status (Supplementary Table S10). Logistic regression models were applied to each imputed and propensity score matched dataset to assess the association between the exposure variables (e.g., hypertension, diabetes, obesity, and smoking) and the outcomes of interest (CAD or ASCVD). Next, these models were adjusted for potential confounders such as age, sex, LDL-C, smoking, hypertension, diabetes, and obesity, depending on the exposure being analysed. The models applied in separate imputation datasets were pooled using Rubin's rules to account for the variability introduced by imputation [13]. All statistical tests are 2-tailed, and a P value < 0.05 was considered statistically significant. All statistical analyses were performed using R, version 4.2.1 (R Foundation, Vienna, Austria).

3. Results

A total of 912 HoFH patients from 43 countries were included. Median age at entry was 33.0 years (IQR 20.0–46.0); 173 (19.0%) were <18 years. 53.3% were female and 60.0% from high-income countries. Median untreated LDL-C was 14.5 mmol/L (11.3 – 18.1), the most recent LDL-C 7.5 mmol/L (4.5 – 11.3)and the lowest on-treatment LDL-C 4.9 mmol/L (2.7 – 7.2). Of 747 patients for whom detailed information on LLT was available, most patients (590 [79.0%]) were on statin therapy, usually high intensity (390 [82.8%] of 419 where statin dosage was available), defined as atorvastatin 40 mg or more or rosuvastatin 20 mg or more per day. Most patients received ezetimibe (57.3%), lipoprotein apheresis (39.9%), and PCSK9 inhibitors (22.1%). Use of lomitapide (8.4%), evinacumab (2.0%), mipomersen (0.8%), and liver transplantation (2.0%) was less frequent. CAD and ASCVD were reported in 30.3% and 36.0% of HoFH patients, respectively (Table 1). Patients with CAD and ASCVD were older than those without, with median ages of 50.0 (IQR 40.0–62.0) and 49.0 years (IQR 39.0–62.0), respectively, compared with 34.0 (IQR 23.0–47.0) and 33.0 years (IQR 22.0–46.0) in those without CAD and ASCVD.

The prevalence of hypertension was 16.5%, diabetes 3.8%, current smoking 8.2%, former smoking 9.8%, overweight 25.4%, and obesity 17.6% (Fig. 1A). Cardiovascular risk factors were more prevalent in older patients (e.g., hypertension: 25.7% in patients ≥30 years vs. 4.3% in patients <30 years; $p < 0.001$) (Fig. 1B), in patients from high-income countries (e.g., hypertension: 17.8% vs. 14.9%; $p = 0.011$) (Fig. 1D), and in those who achieved better LDL-C control (e.g., hypertension: 24.1% in the lowest vs. 14.6% in the highest LDL-C tertile; $p = 0.004$) (Fig. 1C and Supplemental Table S6–S10).

Propensity score matching yielded 157 matched pairs for hypertension, 45 for diabetes, 287 for smoking, and 130 for obesity (Supplemental Table S4), and the matched cohorts were used for subsequent logistic regression analyses. Univariable analysis showed that hypertension was the only risk factor significantly associated with both CAD (OR 1.83, 95% CI 1.15–2.93; $p = 0.01$) and ASCVD (OR 1.84, 95% CI 1.11–3.08; $p = 0.02$) (Table 2, Model 1). After adjustment for age, sex, lowest on-treatment LDL-C, and country-income status (Table 2, Model 2), hypertension remained a significant risk factor for CAD (OR 1.84, 95%CI 1.13–2.99, $p = 0.02$) and ASCVD (OR 1.87, 95%CI 1.09–3.20, $p = 0.03$). Further adjustment for the other risk factors (Table 2, Model 3) confirmed this association for both CAD (OR 1.85, 95%CI 1.11–3.08, $p = 0.02$) (Fig. 1E) and ASCVD (OR 1.78, 95%CI 1.01–3.12, $p = 0.04$) (Fig. 1F). Diabetes, smoking, and obesity were not significantly associated with CAD or ASCVD (Fig. 1E and F). In a complementary analyses in the full multiple imputed cohort, effect estimates were similar to those observed in the propensity score–matched analyses (Supplementary Table S5).

4. Discussion

In this study, hypertension was identified as a significant risk factor for CAD and ASCVD in HoFH patients, while other factors like diabetes, smoking, and obesity were not significantly associated with CAD and ASCVD in this high-risk group. We observed important variation in the prevalence and impact of traditional cardiovascular risk factors across age groups, LDL-C strata and country income levels, supporting the notion that these risk factors may become increasingly relevant as survival in HoFH continues to improve.

The disparities in risk factor prevalence between high- and non-high-income countries underscore the impact of socio-economic conditions on health outcomes in HoFH. In high-income countries, greater access to healthcare and to a greater variety of LLTs could extend lifespan, allowing age-related comorbidities like hypertension, diabetes, and obesity to emerge [14]. Importantly, this pattern should not be interpreted as suggesting that lower on-treatment LDL-C levels are causally associated with a higher burden of traditional risk factors. Rather, it

Table 1
Baseline characteristics.

	Overall (N = 912)
Age of HoFH diagnosis, years	11.0 [6.0 – 25.0]
Age at entry of the registry, years	33.0 [20.0 – 46.0]
Female, N (%)	486 (53.3%)
Male, N (%)	426 (46.7%)
Country income status	
High-income countries	547 (60.0%)
Non-high-income countries	365 (40.0%)
Race [a]	
White	415 (45.5%)
Asian	139 (15.2%)
Black	10 (1.1%)
Other/mixed race	107 (11.7%)
Unknown	241 (26.4%)
Body-mass index, kg/m^2	
Underweight	37 (7.1%)
Normal weight	262 (50.0%)
Overweight	133 (25.4%)
Obesity	92 (17.6%)
Diabetes	30 (3.8%)
Hypertension	132 (16.5%)
Chronic kidney disease	11 (1.7%)
Smoking	
Current smoking	58 (8.2%)
Not current smoker[b]	564 (79.8%)
Lipids, mmol/L	
Untreated	
Total cholesterol	16.0 [12.7 – 20.0]
LDL cholesterol	14.5 [11.3 – 18.1]
HDL cholesterol	1.0 [0.8 – 1.3]
Triglycerides	1.2 [0.9 – 1.8]
Most recent[c]	
Total cholesterol	8.8 [5.8 – 12.9]
LDL cholesterol	7.5 [4.5 – 11.3]
HDL cholesterol	1.1 [0.8 – 1.3]
Triglycerides	1.1 [0.7 – 1.5]
Lowest on-treatment[d]	
Total cholesterol	6.3 [4.2 – 9.1]
LDL cholesterol	4.9 [2.7 – 7.2]
HDL cholesterol	1.0 [0.7 – 1.3]
Triglycerides	0.9 [0.6 – 1.2]
LLT	
Data on LLT available	747 (81.9%)
Statin (%)	590 (79.0%)
High intensity	390 (52.2%)
Moderate intensity	75 (10.0%)
Low intensity	6 (0.8%)
No statin or unknown dose	276 (36.9%)
Ezetimibe (%)	428 (57.3%)
PCSK9 inhibitors (%)	165 (22.1%)
Lomitapide (%)	63 (8.4%)
Evinacumab (%)	15 (2.0%)
Mipomersen (%)	6 (0.8%)
Lipoprotein apheresis (%)	298 (39.9%)
Liver transplantation (%)	15 (2.0%)
CAD	276 (30.3%)
Cardiovascular death	47
Myocardial Infarction	111
Percutaneous Coronary Intervention	226
Coronary Artery Bypass Grafting	142
Age of patients with CAD, years	50.0 (40.0 – 62.0)
Age of patients without CAD, years	34.0 (23.0 – 47.0)
ASCVD	328 (36.0%)
Cardiovascular death	47
Myocardial Infarction	111
Percutaneous Coronary Intervention	226
Coronary Artery Bypass Grafting	142
Stroke	9
Carotid stent	4
Carotid Endarterectomy	15
Peripheral Artery Disease	55
Age of patients with ASCVD, years	49.0 (39.0 – 62.0)
Age of patients without ASCVD, years	33.0 (22.0 – 46.0)

Demographic and clinical characteristics and plasma lipid levels in patients with homozygous familial hypercholesterolaemia. Data are shown as n (%), or median (IQR). HoFH, Homozygous Familial Hypercholesterolemia; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CAD, coronary artery disease; ASCVD, atherosclerotic cardiovascular disease. [¥]Race was reported by the treating physician.

[a] Race was reported by the treating physician.

[b] Not current smoker includes former and never smokers.

[c] This reflects the most recent measurement available after diagnosis and before data entry in the registry.

[d] This reflects the lowest recorded LDL cholesterol measurement between untreated (at diagnosis) and most recent measurement. When unavailable, the most recent measurement itself was considered the lowest.

likely reflects improved survival and healthcare access, permitting the development and detection of age-related comorbidities. Conversely, in non-high-income countries, limited access to as well as underutilisation of LLTs often leads to higher LDL-C levels and earlier CAD events, which may preclude such comorbidities from developing [15]. These observations may also reflect elements of survival bias: patients who develop CAD at a very young age due to extremely high untreated LDL-C levels may not survive long enough to develop traditional risk factors such as diabetes or obesity. This disparity is supported by the markedly earlier manifestation of CAD-related events in non–high-income countries, with median MACE-free survival more than a decade shorter than in high-income countries (24.5 vs 35.0 years; HR 2.01, 95% CI 1.40–2.88) [2]. In addition, improved surveillance and diagnostic capacity in high-income countries likely contributes to higher detection rates of hypertension and diabetes, introducing a potential detection bias.

Previous studies have shown that in patients with HeFH, traditional cardiovascular risk factors, including hypertension, smoking, and obesity, further increase ASCVD risk beyond lifelong exposure to elevated LDL-C (16-21). Our findings suggest that, even in the context of extreme lifelong LDL-C burden in HoFH, hypertension remains associated with elevated cardiovascular risk, underscoring the importance of strict blood pressure control alongside optimal LLT. However, given the substantially earlier disease onset and greater cumulative LDL-C exposure in HoFH, direct extrapolation to HeFH should be made with caution. The absence of independent associations between diabetes, smoking, or obesity and CAD or ASCVD should be interpreted cautiously. The low prevalence of diabetes (3.8%) and current smoking (8.2%), together with the relatively young median age (33 years), likely limited statistical power and reduced cumulative exposure to these risk factors, thereby attenuating detectable associations. In addition, the clinical impact of obesity in youth may differ from that in adults, complicating direct comparisons with older cohorts. Thus, the absence of association should not be interpreted as evidence of absence of effect. Statistical precision was further reduced in the propensity score–matched analyses, particularly for diabetes (45 matched pairs), although effect estimates were directionally consistent with those observed in the full cohort (Supplementary Table S5). The extreme lifelong burden of LDL-C likely accelerates atherosclerosis, compressing the window during which modifiable factors such as diabetes, obesity, or smoking may exert a measurable effect. However, as survival improves through earlier diagnosis and more effective LLT, these factors are likely to also become more relevant. Longitudinal follow-up studies and future cohort expansions are therefore essential to establish whether the contribution of diabetes, smoking, and obesity increases as HoFH patients age and experience longer durations of exposure, and to better clarify temporal relationships and cumulative LDL-C burden across age groups.

4.1. Limitations

This study has several limitations. First, its cross-sectional design precludes inference of temporal or causal relationships between cardiovascular risk factors and ASCVD in patients with HoFH. Cardiovascular risk factors and ASCVD outcomes were recorded at the time of registry entry based on physician-reported data; therefore, the temporal

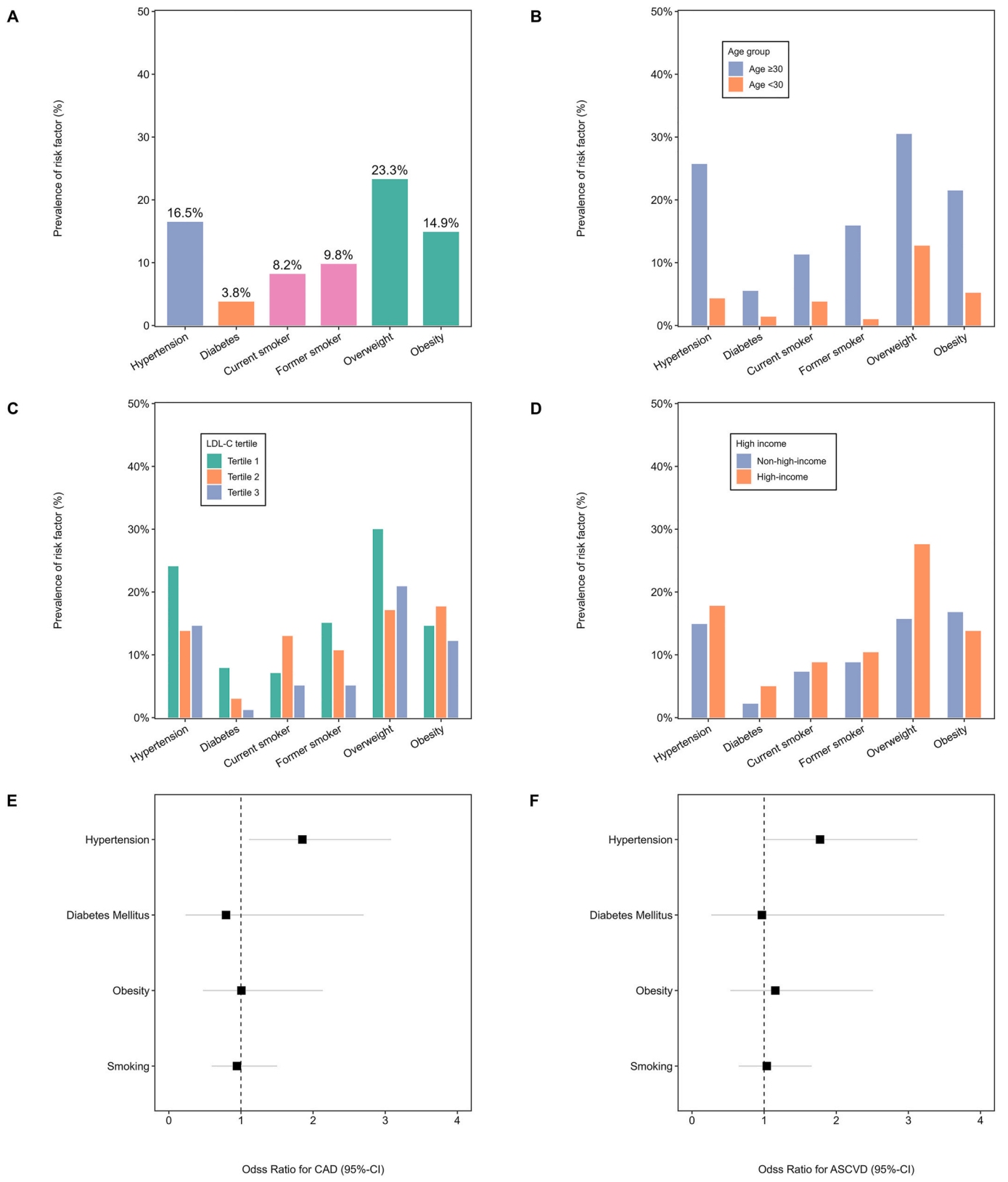

Fig. 1. Prevalence of cardiovascular risk factors and their association with CAD in HoFH patients
The prevalence of the traditional risk factors (Fig. 1A). The prevalence of traditional risk factors stratified by age (Fig. 1B), on-treatment LDL cholesterol tertiles (Fig. 1C) and country income status (Fig. 1D). Hypertension is significantly associated with presence of CAD in HoFH patients, after adjustment for age at entry to the registry, sex, lowest LDL-C and country income status (Fig. 1E) and with presence of ASCVD after adjustment for age at entry to the registry, sex, lowest LDL-C and country income status and the other risk factors (i.e., smoking, diabetes, obesity) (Fig. 1F). Results are presented as odds ratios with 95% confidence intervals. 95%CI, 95% confidence interval.

Table 2
Association of traditional risk factors and coronary artery disease (CAD) and atherosclerotic cardiovascular disease (ASCVD).

	CAD					
	MODEL 1		MODEL 2		MODEL 3	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p-value*
Hypertension	1.83 (1.15 – 2.93)	**0.01**	1.84 (1.13 – 2.99)	**0.02**	1.85 (1.11 – 3.08)	**0.02**
Diabetes	0.91 (0.32 - 2.55)	0.85	0.91 (0.30 – 2.78)	0.87	0.79 (0.23 – 2.70)	0.71
Smoking	0.88 (0.60 - 1.29)	0.51	0.97 (0.62 – 1.51)	0.89	0.94 (0.59 – 1.50)	0.81
Obesity	1.08 (0.55 - 2.14)	0.82	1.06 (0.52 – 2.18)	0.87	1.01 (0.47 – 2.13)	0.99
	ASCVD					
	MODEL 1		**MODEL 2**		**MODEL 3**	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Hypertension	1.84 (1.11 – 3.07)	**0.02**	1.87 (1.09 – 3.20)	**0.03**	1.78 (1.01 – 3.12)	**0.04**
Diabetes	1.02 (0.36 - 2.92)	0.97	1.06 (0.33 – 3.44)	0.92	0.97 (0.27 – 3.50)	0.96
Smoking	0.97 (0.67 - 1.42)	0.89	1.08 (0.69 – 1.69)	0.73	1.04 (0.65 – 1.66)	0.88
Obesity	1.21 (0.59 – 2.44)	0.61	1.12 (0.56 – 2.59)	0.65	1.16 (0.53 – 2.51)	0.72

Model 1: univariate analysis. Model 2: adjustment for age at entry, age at diagnosis, sex, country income status and lowest on-treatment LDL cholesterol. Model 3: model 2 + other risk factors. All estimates are derived from propensity score-matched analyses. Data are shown as odds ratio with 95% confidence interval. OR, odds ratio; 95% CI, 95% confidence interval; CAD, coronary artery disease; ASCVD, atherosclerotic cardiovascular disease. These results are based on baseline data from the propensity score–matched cohort.

sequence between risk factor onset and CAD events cannot be definitively established, and reverse causality cannot be excluded. Hypertension, for example, may have developed after the onset of CAD or in the context of advanced vascular disease or its treatment, and may therefore reflect both a contributing factor and a marker of more severe vascular pathology. Although multivariable adjustment and propensity score matching were applied, residual confounding cannot be excluded. Nevertheless, the consistent association observed across analyses suggests that the presence of hypertension identifies a subgroup of HoFH patients at particularly high cardiovascular risk and may warrant careful clinical attention. Second, the reliance on physician-reported data may introduce reporting bias and variability across centres. Differences in diagnostic practice, screening frequency, and local availability of testing may also have contributed to heterogeneity in the classification of traditional risk factors. Hypertension was recorded without detailed information on blood pressure measurements, duration, or the use, class, or intensity of antihypertensive therapy, limiting a more nuanced assessment of hypertension severity, treatment adequacy, and cumulative exposure. Finally, although this represents the largest global registry of HoFH patients to date, the cohort may not fully reflect patients in regions with limited specialist access, potentially affecting generalizability.

5. Conclusion

In conclusion, hypertension emerged as a significant risk factor independently associated with CAD and ASCVD in patients with HoFH. Its higher prevalence in individuals from high-income countries and those achieving lower LDL-C levels likely reflects increased longevity facilitated by effective LLT and better healthcare access. These findings highlight the importance of addressing not only lifelong hypercholesterolemia but also age-related comorbidities such as hypertension in the comprehensive care of HoFH patients. As survival continues to improve, the role of other traditional cardiovascular risk factors may become more prominent, underscoring the need for ongoing surveillance and longitudinal research.

The authors declare no disclaimers

The funding sources had no role in the design, conduct, or reporting of this study.

Author contributions

WAMS and LFR had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: WAMS, LFR, GKH, DJB, MC, FA, FJR, JRvL, ACF, ALC, ESG, LD, AHZ, TT. Acquisition, analysis or interpretation of data: WAMS, LFR, GKH, DJB, MC, FA, FJR, JRvL, ACF, ALC, ESG, LD, AHZ, TT, HICC collaborators. Drafting of the manuscript: WAMS, LFR. Critical revisions of the manuscript for important intellectual content: GKH, DJB, MC, FA, FJR, JRvL, ACF, ALC, ESG, LD, AHZ, TT, LFR, HICC collaborators. Statistical analysis: WAMS, AHZ, LFR. Supervision: ESG, GKH, LFR.

Financial support

This work was funded by a research grant from Klinkerpadfonds (WAMS and LFR). The HICC is an investigator-initiated project supported by funding from the academic institutions of the collaborators. The European Atherosclerosis Society provided funding to support a registry coordinator. Creation and management of the database was supported in part by NIH/NHLBI grant P01HL059407. The work of Alberico L Catapano has been supported by Italian Ministry of Health - Ricerca Corrente - IRCCS MultiMedica. The data from the Italian cohort of HoFH patients are from the LIPIGEN study. The Austrian Familiar Hypercholesterolemia Registry has been supported by funds form the Austrian Heart Foundation and the Tyrolean Regional Government. The writing committee takes final responsibility for the content of the Article and the decision to submit for publication.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GKH reports that the academic institution has received a research grant from the Klinkerpad fonds for his academic activities, and GKH is employed by Novo Nordisk and has stock in Novo Nordisk, Denmark. DJB reports research grants from Amgen, Amryt, AstraZeneca, Sanofi, and Regeneron; lecture fees and personal fees from Amgen, Amryt, MSD, Sanofi-Aventis and Novartis; participation in advisory board for Amryt (Chair of the LOWER study steering committee); and being a member of the executive committee of the Lipid and Atherosclerosis Society of South Africa and the International Atherosclerosis Society. MC reports receiving grant support for clinical trials from Regeneron Pharmaceuticals and Regenxbio, as well as consulting and lecture fees from Ultragenyx, Chiesi and Regeneron Pharmaceuticals. FA received honoraria related to consulting and speaker activities for Amgen, Novartis and Novo Nordisk. FJR has received research grants, honoraria, or consulting fees for professional input and/or lectures from Amgen, AstraZeneca, MSD, Novartis, Sanofi, Regeneron, Ultragenyx, Chiesi, Cipla, Silence Therapeutics, Verve Therapeutics and LIB Therapeutics. JRvL reports that a research grant from Novartis was received by the

department. ACF reports being co-founder of Goodpath and Avigena, and serving as scientific advisor to MyOme, Arboretum Health, HeartFlow, and Aditum Bio. ALC has received honoraria, lecture fees, or research grants from: Amarin, Amgen, Astrazeneca, Chiesi, Daiichi Sankyo, Eli Lilly, Esperion, Ionis Pharmaceutical, Medscape,Menarini, MSD, New Amsterdam Pharma, Novartis, NovoNordisk, Regeneron, Sanofi, Ultragenyx, Viatris. ESG has received lecturing/ad-board fees paid to his institution from Amgen, Novo Nordisk, Novartis, Ultragenyx, Ionis, Astra-Zeneca and Merck. LD received personal fees for public speaking or consultancy or grant support from Amryt Pharmaceutical, Akcea Therapeutics, Chiesi, Ultragenyx, SOBI, AuroraBiopharma, Novartis, Amarin, Daiichi-Sankyo, Bayer, and Sandoz. LFR is co-founder of Lipid Tools, reports lecture fees from Novartis, Ultragenyx, and Daiichi Sankyo, and advisory board fee from Amgen. The other authors, AHZ, TT and WAMS do not have disclosures for this manuscript.

Acknowledgements

We would like to thank all the participating centres, clinicians, and patients who contributed to this registry. Their collaboration was essential in the development of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2026.120717.

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