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Original Article

Evaluation of cognitive profile and subclinical vascular damage in subjects with genetically confirmed familial hypercholesterolemia

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ABSTRACT

Background: Familial hypercholesterolemia (FH) is characterized by elevated LDL cholesterol (LDL-C) levels that promote atherosclerosis progression. Limited data exist on the link between elevated LDL-C and cognitive impairment. The aim of this study was to assess the prevalence of cognitive impairment in FH subjects and its association with subclinical vascular damage.

Methods: In this cross-sectional observational study, we evaluated 253 genetically confirmed FH subjects aged between 18 and 75 years and without previous documented cognitive disorders. Clinical evaluation, biochemical analyses and vascular profile assessment were obtained from all subjects. Cognitive function was assessed using the Short Blessed Test (SBT). Participants were stratified into two groups according to SBT: normal cognition (NC) group ($n = 202$) and impaired cognition (IC) group ($n = 51$).

Results: The IC group was older and had higher prevalence of hypertension than the NC group. Dutch Lipid Clinical Network (DLCN) score at diagnosis was higher in the IC group than the NC group. Pulse wave velocity (PWV) and intima-media thickness (IMT) were significantly elevated in the IC group than the NC group (PWV: 8.64±0.43 vs 7.24±0.13 m/s, $p = 0.0001$; IMT: 0.78±0.02 vs 0.68±0.01 mm, $p = 0.0003$). Logistic regression showed that cognitive impairment was independently associated with increased PWV (OR 1.32 [1.06–1.66], $p = 0.012$).

Conclusions: FH subjects with cognitive impairment exhibited increased PWV and IMT. These findings suggest that subclinical vascular damage may independently contribute to the cognitive decline in FH subjects.

1. Introduction

Familial hypercholesterolemia (FH) is a genetic lipid disorder characterized by lifelong exposure to high levels of LDL cholesterol (LDL-C), which promotes the progression of atherosclerosis and markedly increases the risk of atherosclerotic cardiovascular disease (ASCVD), especially from early life [1]. Early diagnosis and timely initiation of lipid-lowering therapy (LLT) are crucial for preventing vascular complications and improve long-term outcomes [2]. Beyond its well-established role in ASCVD, elevated LDL-C may also be associated with cognitive impairment in hypercholesterolemic individuals [3].

Several studies have reported a higher prevalence of mild cognitive impairment (MCI) in individuals with FH compared to non-FH controls. Before the age of 40, prolonged exposure to high LDL-C levels may contribute to the development of neurophysiological alterations—such as impairments in executive function, verbal memory, and visuospatial orientation—thereby increasing the risk of early disruption of cortical cognitive processes and the development of MCI in midlife [4–8].

The link between hypercholesterolemia and cognitive decline was first demonstrated in prospective studies involving a large cohort of

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dyslipidemic subjects [9]. These studies found that participants with elevated plasma cholesterol levels (> 240 mg/dL) and high systolic blood pressure (> 160 mmHg) during midlife had a significantly increased risk of developing Alzheimer's disease (AD) in later years. Further evidence comes from a large, longitudinal study by Solomon et al. [10], which followed 9844 men and women from diverse backgrounds over a 30-year period. Unlike previous investigations, this research examined the full spectrum of cholesterol values, categorizing participants into three groups, desirable, borderline, and high. The findings revealed that even moderately elevated cholesterol levels in midlife were associated with a higher risk of developing dementia, including AD, later in life. In addition, FH patients may exhibit a greater frequency of postprandial lipaemia, which has been suggested as a potential risk factor for Alzheimer's disease [11].

Cognitive impairment and dementia are associated with an increased risk of all-cause and cardiovascular mortality. In this context, identifying individuals with possible cognitive decline within high cardiovascular risk populations, such as those with FH, may help detect patients at even greater risk of adverse outcomes. Given that the prevalence of FH is not negligible—traditionally estimated at 1 in 250 for the heterozygous form and 1 in 1000,000 for the homozygous form [12]—and considering the improved survival of these patients thanks to advances in LLTs [13], it is becoming increasingly important to explore the burden of cognitive impairment in this population. To date, however, there is a lack of studies specifically addressing the interplay between cognitive function, cardiovascular risk, and long-term outcomes in FH subjects. Early cognitive assessment could therefore be a valuable tool for identifying vulnerable individuals and investigating potential associations with lipid-lowering strategies and vascular damage.

The aim of this study was to evaluate cognitive function and its determinants, and to assess the relationship between early cognitive impairment and subclinical vascular damage in individuals with FH.

2. Methods

2.1. Study design and population

This was a cross-sectional observational study involving subjects with a probable or defined clinical diagnosis of FH (Dutch Lipid Clinical Network [DLCN] score ≥ 6) who had undergone genetic analysis from July 2016 to December 2024 [14]. All participants were enrolled from the University Hospital of Catania, Italy, a tertiary referral center for the screening, diagnosis and management of familial dyslipidemias [15].

All subjects were aged between 18 and 75 years, free from ASCVD and not receiving LLT at the time of enrollment. The inclusion criteria were (1) genetically confirmed diagnosis of FH due to pathogenic variants and (2) age between 18 and 75 years. The exclusion criteria included: history of ASCVD, presence of neurological or psychiatric disorders, previous head trauma, cerebral haemorrhage, or drug abuse. Subjects receiving LLT at enrollment were also excluded.

After a 12-hour fast, all participants underwent physical examination and review of clinical history, as well as biochemical analyses, cognitive function assessment using the Short Blessed Test (SBT), and evaluation of vascular profile using carotid ultrasound and pulse wave velocity (PWV) [16].

Arterial hypertension was defined as brachial blood pressure (BP) ≥ 140 mm Hg (systolic) and/or 90 mm Hg (diastolic) on at least two different occasions, or if the subject was on antihypertensive therapy [17]. Body weight and height were measured, and body mass index (BMI) was calculated as weight (kg) divided by [height (m)]^2 [18]. Type 2 diabetes (T2D) was defined as a fasting plasma glucose (FPG) ≥ 126 mg/dL on two consecutive measurements and/or glycated haemoglobin (HbA1c) ≥ 6.5 %, or the use of antidiabetic medications [19]. Smoking status was categorized as current smoking (defined as at least one cigarette in the last month) or not [20].

ASCVD was defined as documented history of myocardial infarction, acute coronary syndrome, coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery), stroke or transient ischemic attack, peripheral arterial disease, or other arterial procedures [21].

Participants were stratified into two groups based on the SBT result: FH subjects with normal cognition (NC group, 202 subjects with a SBT score of 0–4) and FH subjects with impaired cognition (IC group, 51 subjects with a SBT score ≥ 5).

The study was approved by the local ethics committee in accordance with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from each subject enrolled in the study.

2.2. Biochemical analyses

FPG was measured with the glucose oxidase enzymatic method. Serum total cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL-C), high sensitive c-reactive protein (hs-CRP), and creatinine were assessed using currently available enzymatic methods [22]. LDL cholesterol (LDL-C) concentrations were estimated using the Friedewald formula. Estimated glomerular filtration rate (eGFR) was assessed with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [23].

HbA_{1c} was measured via high performance liquid chromatography using a National Glycohemoglobin Standardization Program and was standardized to the Diabetes Control and Complications Trial (DCCT) [24] assay reference. Chromatography was performed using a certified automated analyser (HLC-723G7 haemoglobin HPLC analyser; Tosoh Corp.) (normal range 4.25–5.9 %).

2.3. Short blessed test

The SBT is a 6-item orientation-memory concentration test that has been validated as a measure of cognitive impairment and has been shown to discriminate among mild and severe cognitive deficits [25].

Based on clinical research findings from the Memory and Aging Project, the following cut points may also be considered: 0 – 4 Normal Cognition; 5 – 9 Questionable Impairment (evaluate for early dementing disorder); 10 or more Impairment Consistent with Dementia (evaluate for dementing disorder). While in other cognitive tests the level of education influences the performance of the cognitive assessment, the SBT is not sensitive to the level of education [26].

2.4. Carotid ultrasound examination

Ultrasound scans were performed using a high-resolution B-mode ultrasound system. Briefly, all ultrasound examinations were performed by a single physician who was blinded to the clinical and laboratory characteristics of the patients. Longitudinal B-mode (60 Hz, 128 radiofrequency lines) images of the right common carotid artery 2 cm below the carotid bulb were obtained using a high-precision echo tracking device (MyLab Alpha, Esaote, Maastricht, NL) paired with a high-resolution linear array transducer (13 MHz) to acquire intima-media thickness (IMT) using the built-in echo tracking software [27].

2.5. Pulse wave velocity

The SphygmoCor CvMS (AtCor Medical, Sydney, Australia) system was used for the determination of PWV. This system uses a tonometer and two different pressure waves obtained at the common carotid artery (proximal recording site) and at the femoral artery (distal recording site). An electrocardiogram was used to determine the start of the pulse wave. The PWV was determined as the difference in travel time of the pulse wave between the two different recording sites and the heart, divided by the travel distance of the pulse waveform. The PWV was

calculated on the mean basis of 10 consecutive pressure waveforms to cover a complete respiratory cycle.

2.6. Statistical analyses

The sample size was calculated based on PWV using a level of significance (α) set to 5 % and a power (1-β) set to 80 %, with an estimated difference of PWV of 2 m/s between Normal and Impaired cognition groups [28]. The estimated sample size was a minimum of 50 patients per group. The distributional characteristics of each variable, including normality, were assessed using the Kolmogorov–Smirnov test. Data are reported as mean ± standard deviation (SD) for continuous parametric and median (interquartile range-IQR) for continuous non-parametric variables and as frequency (percentage) for categorical variables. When necessary, continuous non-parametric variables (TG, hs-CRP) were logarithmically transformed for statistical analysis to reduce skewness. The Chi square ($\chi 2$) test was used for categorical variables. To test differences in clinical and biochemical characteristics between the groups Student's *t*-test was used. In order to identify a relationship between clinical variables and the impaired cognitive function, a multivariate logistic regression analysis was performed. Model 1 included age and sex. Model 2 added BMI, active smoking, LDL-C, hypertension, HbA1c, and DLCN score. Finally, Model 3 incorporated PWV. Variables that were statistically significant in the previous model were retained in the subsequent model. Prior to multivariate analyses, variance inflation due to covariates was verified and any variable with a variance inflation factor (VIF) > 2 was excluded from the analysis. No variables exceeded this threshold, indicating an acceptable level of collinearity in the models. All statistical analyses were performed using R 4.4.1 Statistics for Windows version 23. For all tests, a $p < 0.05$ was considered significant.

3. Results

In total, 521 subjects were evaluated; of these, 253 genetically confirmed FH subjects satisfied the inclusion criteria and participated in this study (Fig. 1).

Table 1 shows the characteristics of the study population stratified according to cognitive function. The IC group was older than the NC group (53.06 ± 17.79 vs. 45.77 ± 18.35 years, $P = 0.022$) while BMI as well as the prevalences of males, smokers, and diabetes were similar between the two groups. Hypertension was significantly more frequent among participants with IC compared to those with NC (29.4 % vs. 11.8 %, $P = 0.003$).

HDL-C levels as well as TG, Lp(a), HbA1c, FPG, serum creatinine, and hs-CRP levels were similar between the two groups.

DLCN score as well as TC and LDL-C were higher in the IC group than the NC group (DLCN score: 8.11 ± 3.52 vs. 6.75 ± 3.22; TC: 354.37 ±15.81 vs 332.55±16.70; LDL-C: 276.95 ± 16.72 vs. 251.80 ± 15.69 mg/dL; for both $p < 0.05$). All subjects were heterozygous FH and the most frequent genetic variant was the LDL receptor (LDLR) mutation. **Supplementary Table 1** shows the genetic profile of the study population.

Fig. 2 illustrates the distribution of subclinical vascular damage within the two groups. The IC group showed higher values of PWV compared with the NC group (8.64 ± 0.43 m/s vs. 7.24 ± 0.13 m/s, $P < 0.001$). Mean carotid IMT was increased in the IC group compared with NC group (0.78 ± 0.02 vs 0.68 ± 0.01 mm, $P < 0.001$).

As demonstrated in Fig. 3, multivariate logistic regression analyses were performed to identify factors independently associated with

Table 1
Clinical characteristics of the Study Population stratified according to the cognitive function.

	Normal Cognition (n = 202)	Impaired Cognition (n = 51)	Total (n = 253)	p-value
Age, years	45.77±6.35	53.06±6.79	47.25±6.44	<0.05
Males, n (%)	107 (53.0)	21 (41.2)	128 (50.6)	0.13
Smoking, n (%)	47 (35.3)	9 (24.3)	56 (32.9)	0.21
T2D, n (%)	4 (3.1)	2 (5.6)	6 (3.6)	0.47
BMI, kg/m^2	25.16±3.66	25.88±4.10	25.32±3.76	0.31
Hypertension, n (%)	24 (11.8)	15 (29.4)	39 (15.4)	0.003
DLCN score at diagnosis	6.75±3.22	8.11±3.52	7.00±3.31	<0.05
TC, mg/dl	332.55±16.70	354.37±15.81	342.51 ±16.62	<0.05
HDL-C, mg/dl	53.88±9.02	51.07±8.42	53.31±9.27	0.19
LDL-C, mg/dl	251.80±15.69	276.95±16.72	257.20 ±16.62	<0.05
TG, mg/dl	81 (64–99)	83 (72–106)	81 (64–102)	0.85
Lp(a), mg/dl	31.98 ± 5.2	26.66 ± 6.3	30.23 ± 4.8	0.48
HBA1c, %	5.49±0.41	5.55±0.43	5.50±0.42	0.47
FPG, mg/dl	87.18±11.72	91.17±11.76	88.03 ±11.81	0.076
Creatinine, mg/dl	0.77±0.17	0.73±0.14	0.76±0.16	0.27
hs-CRP, mg/dl	0.09 (0.05–0.19)	0.12 (0.05–0.23)	0.1 (0.05–0.21)	0.89
SBP, mmHg	117±15	119±16	117±15	0.92
DBP, mmHg	70±10	69±11	69±10	0.89

Data are presented as mean ± SD, median (IQR), or percentage. T2D: type 2 diabetes; BMI: body mass index; DLCN: Dutch Lipid Clinical Network; TC: total cholesterol; HDL: HDL-C cholesterol; LDL-C: LDL cholesterol; TG: triglycerides; Lp(a): lipoprotein(a); HbA1c: glycated hemoglobin; FPG: fasting plasma glucose; hs-CRP: high sensitive c-reactive protein; SBP: systolic blood pressure; DBP: diastolic blood pressure. DLCN was calculated prior to genetic analysis. TC, LDL-C, HDL-C and TG were evaluated at diagnosis.

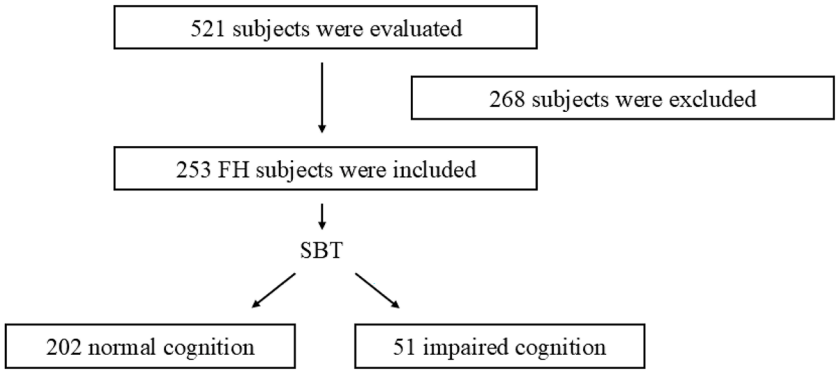

Fig. 1. Enrollment flowchart of the study population.
Enrollment flowchart. Based on the Short Blessed Test (SBT), 202 (79.8 %) individuals were classified as having normal cognition and 51 (20.2 %) as having impaired cognitive function. FH: familial hypercolesterolemia.

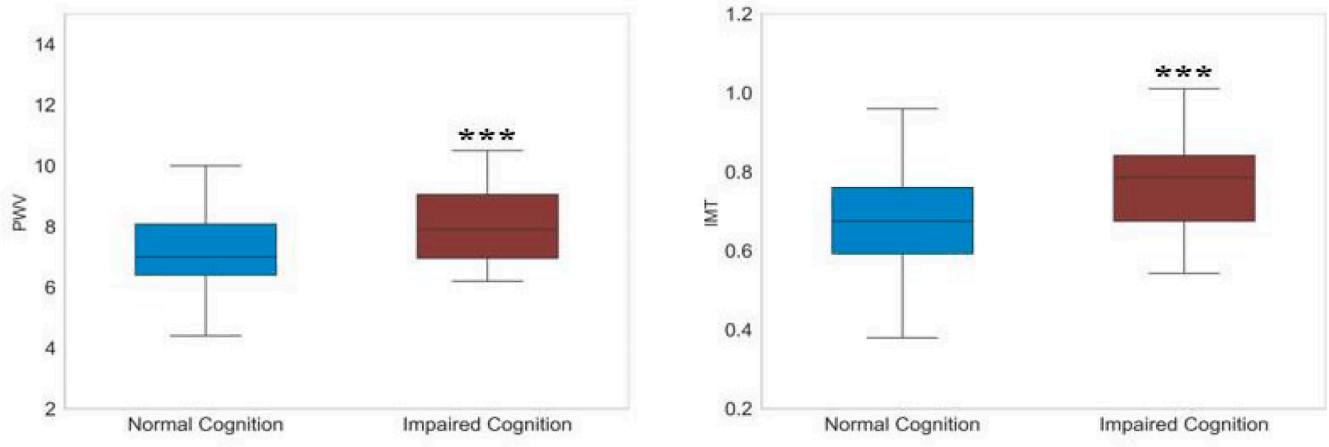

Fig. 2. Subclinical vascular damage in the Study Population stratified according to the cognitive function.
Pulse wave velocity (PWV) and carotid intima-media thickness (IMT) were significantly higher in patients with impaired cognition compared to those with normal cognitive function. Data are presented as mean ± SD. *** $P < 0.001$.

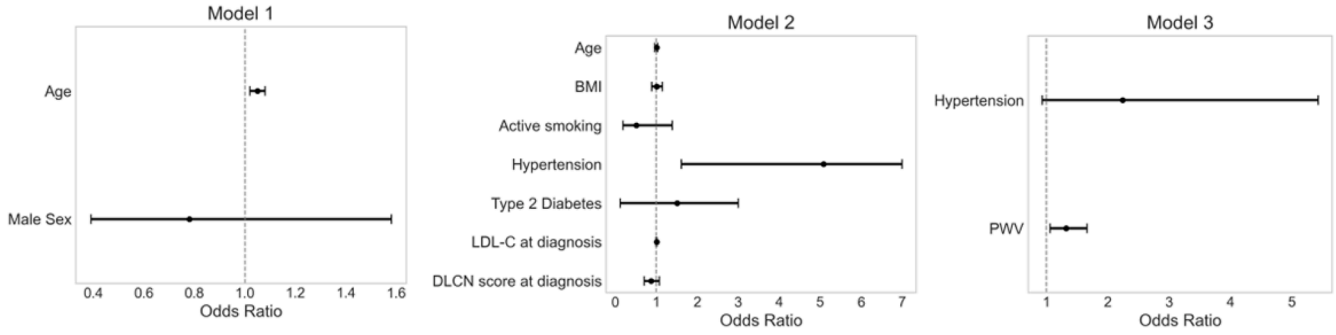

Fig. 3. Multivariate Logistic Regression Models for Cognitive Status in Patients with Familial Hypercholesterolemia.
Forest plots showing the odds ratios (ORs) and 95 % confidence intervals (CIs) from three consecutive multivariate logistic regression models evaluating factors associated with impaired cognitive function in patients with familial hypercholesterolemia (FH). Model 1 includes age and sex. Model 2 includes age, BMI, active smoking, LDL-C at diagnosis, hypertension, DLCN score at diagnosis, and diabetes. Model 3 includes hypertension and pulse wave velocity (PWV). *$P < 0.05$.

cognitive status. In Model 1, age was significantly associated with impaired cognition (OR 1.05, 95 % CI 1.02–1.08, $P = 0.04$). In Model 2, hypertension (OR 5.08, 95 % CI 1.6–16.1, $P = 0.006$) was independently associated with impaired cognitive function. Finally, Model 3, which included PWV, showed that PWV (OR 1.32, 95 % CI 1.06–1.66, $P = 0.012$) was independently associated with impaired cognition.

4. Discussion

In this cross-sectional study, we investigated the distribution of cognitive impairment and subclinical vascular damage in FH subjects. We found that impaired cognitive function, as assessed by the SBT, was present in 20 % of the study population. This suggests that the prevalence of cognitive impairment may be higher in FH subjects compared to the general population of similar age. Indeed, in the meta -analysis by Pais et al., the prevalence of cognitive impairment ranged between 6.5 % and 34.5 % (median 12 %) among individuals aged 50–59 years, and between 5.1 % and 37.5 % (median 20.1 %) among those aged 60–69 years in a community-based sample [29]. Considering that the mean age of our FH cohort was in the mid-50 s, the 20 % prevalence we observed appears higher than the expected median values for this age group. Moreover, Zambon et al. reported a significantly higher prevalence of mild cognitive impairment in FH patients compared to matched non-FH controls (21.3 % vs 2.9 %) [30]. In this context, our findings suggest that cognitive dysfunction may already be present in middle-aged individuals with FH, highlighting the need for early screening strategies. One possible explanation for this early cognitive impairment is the cumulative exposure to elevated LDL-C levels throughout life. In individuals with FH, the lifelong burden of high LDL-C has been associated with early and accelerated atherosclerotic processes, which may also affect the cerebral vasculature [31]. Chronic endothelial dysfunction, microvascular damage, and impaired cerebral perfusion may, over time, contribute to subtle but clinically relevant neurocognitive decline. Therefore, the cumulative LDL-C burden could represent a key factor linking hypercholesterolemia to early cognitive impairment [32].

In the present study, participants with impaired cognition exhibited higher baseline LDL-C levels and a higher DLCN score compared with the normal cognition group; thus, the prolonged exposure to high LDL-C levels could contribute to cognitive function impairment. In line with our findings, previous studies reported an association between higher LDL-C levels and cognitive impairment [33,34]. For example, the ELSA-Brasil cohort showed a relationship between baseline LDL-C and cognitive decline, including impairments in memory, verbal fluency, and global cognition. Interestingly, these associations were more pronounced in individuals under the age of 60, suggesting that lipid-related cognitive impairment may manifest earlier in FH subjects. Moreover, in the ARIC study, greater cumulative exposure to elevated LDL-C levels during midlife was associated with an increased risk of cognitive impairment and dementia. These findings support the hypothesis that early identification of a more severe FH phenotype could help detect individuals at higher risk for cognitive dysfunction, who may benefit from cognitive monitoring in addition to optimized lipid-lowering

therapy.

Importantly, in our study we observed that PWV and IMT — markers of subclinical vascular damage — were significantly elevated in FH subjects with impaired cognition; for comparison, a hospital-based age-matched reference cohort reported lower PWV and IMT values in non-FH subjects (PWV: 6.68 ± 0.73 m/s; IMT: 0.71 [0.60–0.75] mm) [35,36]. Finally, in multivariate logistic regression analyses, age was significantly associated with impaired cognition in Model 1. However, in the fully adjusted Model 3, which included PWV and other confounders, PWV remained independently associated with impaired cognition, whereas age was no longer significant. This indicates that although age contributes to cognitive differences, vascular factors such as PWV play a key independent role in this cohort.. These findings suggest that mechanical vascular impairment may play a key role in the cognitive impairment observed in FH subjects.

Our results are consistent with previous studies evaluating the association between PWV and cognitive dysfunction. Pase et al. reported a significant inverse relationship between PWV and global cognitive performance, executive function, and memory, independent of demographic and cardiovascular risk factors in a systematic review and meta-analysis [37]. Scuteri et al. reported that increased PWV was an independent predictor of longitudinal cognitive decline in a cohort of community-dwelling older adults without baseline dementia [38]. Furthermore, Wang et al. showed that increased carotid IMT was associated with poorer cognitive performance in multiple domains, including attention and memory, in a cross-sectional study of middle-aged and older community-dwelling adults [39].

Finally, among traditional cardiovascular risk factors, hypertension emerged as an independent predictor of cognitive impairment in line with previous findings on the role of elevated blood pressure in the development of vascular cognitive impairment and dementia [40]. Chronic hypertension contributes to microvascular damage, white matter lesions, and cerebral hypoperfusion that promote cognitive dysfunction progression. These findings highlight the importance of optimal blood pressure control for reducing the cognitive impairment FH subjects.

Our study presents some limitations. First, this was a cross-sectional study; thus, a longitudinal causal relationship cannot be established. Second, cognitive function was assessed using the SBT, a brief screening tool that may not capture subtle or domain-specific deficits. Although the SBT is widely used and has been validated for the detection of general cognitive impairment, it does not provide the detailed domain-specific assessment offered by more comprehensive tools such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA). Moreover, the commonly used SBT cut-offs were validated in elderly cohorts, and in younger adults the test may show a floor effect, limiting its sensitivity to subtle cognitive differences. Future studies employing comprehensive neuropsychological assessments could provide a more detailed cognitive profile evaluation in this population. Third, potential confounding factors such as education, physical activity, and diet were not available and may influence both vascular health and cognitive function. Fourth, we did not evaluate the presence of carotid atherosclerotic plaques, which are an established marker of vascular damage and may be associated with cognitive impairment. Including this parameter in future studies could improve the understanding of the vascular contribution to cognitive decline in FH subjects. Finally, we did not include a non-FH reference population, which limits the comparisons to general population.

Therefore, further longitudinal studies with larger samples, more detailed neurocognitive testing, and a broader assessment of vascular biomarkers, including carotid plaque evaluation, are necessary to confirm and expand our findings. In addition, advanced neuroimaging approaches, such as cerebral Magnetic Resonance Imaging (MRI) and β-amyloid imaging, would be useful to further characterize the mechanisms underlying cognitive impairment in FH. Another important aspect that warrants further investigation is the potential role of the apolipoprotein E (apoE) genotype, since the presence of the apoE4 allele has been consistently associated with an increased risk of cognitive decline in the general population [41]. Future studies evaluating the role of ApoE isoforms in a cohort of FH subjects with a cognitive impairment are needed.

From a clinical perspective, our findings suggest that in FH subjects cognitive impairment is more likely related to subclinical vascular injury than to a primarily degenerative process. Thus, an early and intensive LLT as well as an aggressive control of the other traditional cardiovascular risk factor are needed; moreover, the implementation of cognitive screening in routine care could be useful to better identify FH subjects with impaired vascular and cognitive profile.

In conclusion, an early cognitive impairment was present in 20 % of FH subjects and higher LDL-C and DLCN score as well as increased PWV and IMT were observed in patients with impaired cognition. The identification of worse clinical and vascular profiles could be useful to early detect FH subjects with an impaired cognitive function who may benefit from early cognitive monitoring over the optimization of lipid lowering therapy. Further studies are needed to evaluate the role of atherosclerotic burden in cognitive impairment.

List of abbreviations

AD	Alzheimer's disease
BMI	Body mass index
BP	Systolic blood pressure
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DLCN	Dutch Lipid Clinical Network
hs-CRP	high sensitive c-reactive protein
eGFR	Estimated glomerular filtration rate
FH	Familial hypercholesterolemia
FPG	fasting plasma glucose
HDL-C	HDL cholesterol
HR	Hazard ratio
HbA1c	Glycosylated hemoglobin
IMT	Intima-media thickness
LDL-C	LDL cholesterol
LLT	lipid lowering therapy
MCI	mild cognitive impairment
PWV	Pulse wave velocity
SBT	Short Blessed Test
TC	total cholesterol
TG	triglycerides

Authors' contributions

S.S. contributed to the study design, researched data, contributed to the discussion, and wrote the article. M.D.M., N.M., S.C., M.M., G.B., F. D.G.B., C.P., M.M., M.T., A.R., M.C.P., C.I. researched data, contributed to the discussion, and reviewed and edited the article. A.D.P., S.P. contributed to the study design and discussion, and reviewed and edited the article. contributed to the discussion. R.S. designed the study, researched data, contributed to the discussion, and reviewed and edited the article.

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Research involving human participants and/or animals

This study was approved by the local ethics committee in accordance with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent

Informed consent was obtained from each participant enrolled in the study.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

Acknowledgement

S.P. is the guarantor of this work and, as such, 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. All authors approved the final version. Genetic analysis was carried out within the Lipigen study, an initiative of the SISA Foundation supported by an unconditional research grant from Sanofi; the genetic assessment was performed in collaboration with GenInCode, Barcelona, Spain.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2025.106511.

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