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Serum HDL-cholesterol is associated with the clinical-biological profile of early-stage Parkinson's disease patients independently of APOE

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ABSTRACT

Emerging evidence highlights a possible interplay between serum lipid profiles and Parkinson's disease (PD), but the biological underpinnings remain largely unexplored. In this cross-sectional study, we investigated whether serum lipid levels (total cholesterol, high-density lipoprotein cholesterol (HDL), non-high-density lipoprotein cholesterol, and triglycerides) were associated with clinical severity and cerebrospinal fluid (CSF) biomarkers in early-stage PD patients. A cohort of 90 PD patients and 74 matched controls underwent serum lipid and CSF biomarker assessment and *APOE* genotyping. While serum lipid levels did not differ significantly between groups, PD patients showed reduced CSF α-synuclein. Notably, higher HDL levels correlated with higher CSF α-synuclein and amyloid-β42 (Aβ42) concentrations and milder motor impairment, independent of *APOE* ε4 status. *APOE* ε4 carriers displayed increased CSF phosphorylated tau and reduced Aβ42/Aβ40 ratio, but *APOE* genotype did not modify the observed HDL associations. These findings suggest that higher circulating HDL levels are associated with a milder clinical phenotype and a more favorable CSF biomarker profile in early-stage PD, potentially reflecting a protective role independent of *APOE* genotype. Further studies are warranted to validate these observations and to assess their therapeutic implications.

1. Introduction

Parkinson's disease (PD) is a common, clinically heterogeneous, neurodegenerative disorder whose neuropathological hallmarks encompass the loss of dopaminergic nigral neurons and the brain accumulation of α-synuclein (α-syn) enriched Lewy's bodies (Hayes, 2019). PD pathogenesis is complex and involves the disruption of multiple biological pathways (Liddle, 2018; Tansey et al., 2022).

In recent years, lipids have emerged as critical in these mechanisms (Alecu and Bennett, 2019). Lipids and lipoproteins, namely the molecular complexes transporting the lipids across body fluids, have multiple roles in the central nervous system, such as influencing the synapse's flexibility and regulating intracellular signaling (Dai et al., 2021; Wei et al., 2023; Yoon et al., 2022).

In PD, lipid dysmetabolism has been linked to the core neuropathology, including α-synucleinopathy and mitochondrial dysfunction (Kamano et al., 2024; Lu et al., 2021). Moreover, the high-density lipoproteins (HDL), which allow for the transportation of excessive cholesterol from the peripheral tissues to the liver, participate in systemic inflammation that is also critical in PD, acting as an anti-inflammatory factor (Gordon et al., 2011; van der Vorst, 2020; Yacoubian et al., 2023).

The relevance of lipids to PD has been further underlined by several studies estimating the disease risk due to blood cholesterol and triglyceride levels (Hong et al., 2022; Hurh et al., 2022; Jiang et al., 2020). Moreover, different clinical studies have investigated the link between

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serum lipid profiles and PD severity, although findings have often been inconclusive or contradictory. Some reports have demonstrated negative correlations between total cholesterol, low-density lipoprotein, or HDL levels and PD motor/cognitive impairment (Jeong et al., 2023; Yang et al., 2020), while others have observed no significant relationships or have identified different lipid fractions to be relevant (Gu et al., 2024). However, the biological bases of this association have been poorly investigated in patients since most of the evidence in this regard comes from experimental models.

Apolipoprotein E (*APOE*) has been widely recognized as a crucial genetic factor in various neurodegenerative conditions, including PD (Liampas et al., 2024; Liu et al., 2013a; Pu et al., 2022). *APOE* encodes a protein essential for lipid transport and metabolism, facilitating the distribution and clearance of cholesterol and other lipids in both peripheral tissues and the central nervous system (Huang and Mahley, 2014; Yang et al., 2023). Different *APOE* alleles modify the risk and the progression of neurodegenerative disease by influencing processes such as amyloid aggregation, inflammation, and synaptic maintenance(Liu et al., 2013b), thereby underscoring the intersection between *APOE*--driven lipid homeostasis and the pathological pathways in PD.

Measurement of neurodegeneration CSF biomarkers, such as total α-syn, amyloid-β peptides, and tau proteins, allows for tracking in vivo pathological events underlying PD (Sancesario et al., 2020; Schirinzi et al., 2019). Accordingly, here, we attempted to dissect in vivo the interplay between serum lipid levels and the clinical-biological profile of PD by examining the correlations between cholesterol (total, HDL, NonHDL), triglycerides, and the neurodegeneration CSF biomarkers in a well-characterized early-stage PD population, stratified per *APOE* status.

2. Materials and methods

2.1. Study population and clinical assessment

This study included 90 patients with early-stage PD (disease duration < 3 years and levodopa equivalent daily dose (LEDD) < 300) and 74 age/sex-matched controls (CTRL), recruited from the Neurology Unit of Tor Vergata University Hospital in Rome, Italy. PD was diagnosed according to the 2015 Movement Disorder Society (MDS) criteria (Postuma et al., 2015). CTRL were patients without neurodegenerative diseases receiving lumbar puncture for diagnostic purposes (e.g., functional disorders or suspected inflammatory disease); none of the CTRLs had significant cognitive decline (Mini-Mental State Examination >= 24). The exclusion criteria were: 1) main acute/chronic inflammatory/infectious diseases; 2) history of diabetes mellitus; 3) hypolipidemic therapy or a history of familial dyslipidemias; 4) other neurodegenerative diseases or movement disorders.

Demographic, anthropometric, and medical history data were recorded for each participant. PD patients were assessed using the Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale part III (MDS-UPDRSIII), the Hoehn and Yahr (H&Y) scale, Mini-Mental State Examination corrected for age and educational level (MMSE), and the Non-Motor Symptoms Scale (NMSS). The personal LEDD was calculated using the conventional formula (Tomlinson et al., 2010). Expert personnel performed clinical assessment within one week of blood/CSF sampling.

The study was approved by the local ethics committee (protocol n° 16.21) and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

2.2. Serum lipid measurement

All participants underwent venous blood sampling for serum lipid measurement in the morning after overnight fasting. Biochemical parameters were measured on venous blood. The collected sera were centrifuged for 10 min at 2000 × g and then processed as fresh samples to allow for clot formation. All tests were performed and interpreted in accordance with the manufacturer's instructions. Serum samples were analyzed for lipid profiles, including high-density lipoprotein cholesterol (HDL), total cholesterol (TC), and triglycerides (TG). Non-high-density lipoprotein cholesterol (NonHDL) was calculated by subtracting HDL cholesterol from the total cholesterol levels (Blaha et al., 2008). All these tests were measured with an immunoturbidimetric method with the Alinity Analyzer (Abbott Diagnostics, Chicago, IL, USA).

2.3. CSF biomarkers assay and ATN profile

A lumbar puncture was performed within one week of the lipid profile analysis and the clinical assessment. The levels of amyloid-β42 (Aβ42), amyloid-β40 (Aβ40), total tau (t-tau), phosphorylated-181-tau (p-tau), were measured using fully-automated CLEIA Fujirebio LUMIPULSE® G1200 (Fujirebio, Inc., Tokyo, Japan); and the levels of total α-syn were assessed using Human α-synuclein ELISA kit (Biolegend). The amyloid-β42/amyloid-β40 ratio (Aβ42/Aβ40) was calculated as previously described (Nakamura et al., 2018).

According to CSF Aβ42/Aβ40, p-Tau levels, and t-Tau levels, patients were stratified based on the AT(N) framework (Jack et al., 2018), a classification approach that has gained increasing attention due to the recognized role of Alzheimer's disease co-pathology in synucleinopathies (Barba et al., 2024). Among the 90 PD included, one patient showed an A+T + N + profile, three showed A−T+N+ profiles, four had A−T+N+, five had A−T+N+, and four were classified as A+T−N−, while the remaining 73 patients presented an A−T − N − profile. Due to the small number of patients in each subgroup except A-T-N-, no further stratified analyses were conducted, given the lack of statistical power.

2.4. APOE genotyping

Genomic DNA was extracted from blood, and the *APOE* genotype was determined by the AMPLI-ApoE T334C and C472T kit, which allows the detection of the presence of the 334T/C and 472C/T polymorphisms responsible at the protein level for the amino acid variants C112R and R158C. These polymorphisms are searched for after amplification with specific primers and hybridization with a probe that recognizes an internal sequence. The probe is labeled with two different fluorophores (reporter dye and quencher dye). During the amplification reaction, the release of the quencher from the probe causes an increase in fluorescence caused by the reporter, which is, therefore, directly proportional to the amount of amplified product recognized (real-time quantitative PCR; CFX96 Real-Time System; BIORAD). According to the *APOE* genotype, participants were grouped into "ε4" carriers (when carrying at least 1 copy of the ε4 allele) and "non ε4" carriers (when carrying ε2 and ε3 alleles and no ε4 alleles). Since we found only n = 4 ε2 carriers, further stratification by individual *APOE* genotypes was not feasible. Therefore, we adopted a binary classification, as previously done in similar studies (Zenuni et al., 2023).

2.5. Statistical analysis

The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Variables that deviated from normality were log10-transformed before statistical analysis to meet the assumptions required for parametric tests. Group comparisons were performed using ANCOVA or Chi-square tests, as appropriate, with adjustments for age and sex when applicable. Pearson's partial correlation analysis, adjusted for age and sex, was employed to explore the relationships between serum lipid profiles, clinical characteristics, and biological markers in both cohorts. Although the PD and CTRL groups were matched for age and sex, these variables were included as covariates in statistical analyses to reduce residual confounding and variance and to address the potential *per se* effect of these biological factors on the lipid profile. Moreover, we computed the out-of-sample performance of Pearson's

partial correlations using bootstrapping (BS) as a cross-validation (CV) method. This resampling technique allowed us to assess the reliability of our correlation estimates by repeatedly sampling subsets of the data. The number of BS iterations we used was 1000. In the results, we provided a 95 % confidence interval (BS-95 %CI) of the BS distribution of correlation coefficients as an estimation of the robustness of our findings. Finally, the false Discovery Rate (FDR) method was employed to control the family-wise error rate (FWER). Additionally, we performed multiple linear regression analyses to further investigate the associations between serum lipid profile and selected clinical and biological markers. The dependent variables included in the models were chosen based on significant associations observed in partial correlation analyses. All regression models included age, sex, and *APOE* genotype as covariates. Statistical significance was defined as $p \leq 0.05$, and all analyses were conducted using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Group analysis

Table 1 summarizes the study population's demographic, clinical, and biochemical features.

PD patients exhibited lower CSF α-syn levels (897.60 ± 327.3 pg/mL) than CTRL (1164.21 ± 505.6 pg/mL; $p < 0.01$). Other CSF biomarkers and serum lipid levels did not differ between the two groups. An overview of the group comparisons for serum lipid levels and CSF biomarkers is provided in Fig. 1.

In the PD group, *APOE* ε4 carriers (n = 13) showed higher CSF p-Tau levels (52.3 ± 30.2 pg/mL) compared to non-carriers (27.9 ± 12.0 pg/mL; ANCOVA on log10-transformed values, $p < 0.01$) and lower Aβ42/Aβ40 (0.11 ± 0.3 vs 0.15 ± 0.4; $p = 0.03$). Other CSF biomarkers (t-tau, α-syn) and serum lipid levels did not differ significantly between *APOE* ε4 carriers and non-carriers. In the CTRL group, no significant differences were found between *APOE* ε4 carriers (n = 11) and non-carriers concerning either serum lipid profiles or CSF biomarker concentrations.

3.2. Partial correlation analysis

We performed a partial correlation analysis using sex and age as covariates. In the PD group, we found significant partial correlations between HDL and α-syn (r = 0.35, pFDR = 0.02, BS-95 % CI [0.10, 0.68]), HDL and Aβ42 (r = 0.30, pFDR = 0.04, BS-95 % CI [0.06, 0.65]), HDL and Aβ42/Aβ40 (r = 0.36, pFDR = 0.03, BS-95 % CI [0.04, 0.55]), and HDL and MDS-UPDRSIII (r = -0.32, pFDR = 0.02, BS-95 % CI [-0.58, 0.02]) (Fig. 2). Conversely, no significant partial correlations were observed in the CTRL group.

After further adjusting for *APOE ε4* carrier status, the previously identified significant partial correlations between HDL and CSF biomarkers (α-syn, Aβ42, Aβ42/Aβ40) and clinical severity (MDS-UPDRSIII) remained statistically significant (all pFDR <0.05), suggesting that these relationships were not mediated by *APOE* genotype. These results are graphically presented in Supplementary Figure 1.

Table 1
Demographic, clinical, and biochemical features of the population of the study.

Variable	PD patients (n = 90)	CTRL (n = 74)	*P value*
Age (y)	61.5 ± 10.2	62.1 ± 11.3	n.s.
Sex (male/female)	65/25	44/30	n.s.
Disease duration(y)	1.6 ± 0.9	\	\
BMI	26.4 ± 2.6	\	\
HDL (mg/dl)	49.5 ± 8.7	47.5 ± 10.6	n.s.
TC (mg/dl)	180.6 ± 31.6	177.6 ± 35.8	n.s.
NonHDL (mg/dl)	122.5 ± 32.2	130.0 ± 36.5	n.s.
TG (mg/dl)	103.9 ± 54.6	110.8 ± 45.4	n.s.
MDS-UPDRSIII	25.4 ± 9.8	\	\
MMSE	28.0 ± 1.7	26.9 ± 2.1	\
NMSS	34.6 ± 33.0	\	\
H&Y	1.9 ± 0.6		\
LEDD	50.8 (±104.7)		\
Aβ42 (pg/mL)	914.5 ± 327.4	981.2 ± 469.7	n.s.
Aβ42/Aβ40	0.14 ± 0.04		\
t-Tau (pg/mL)	245.3 ± 125.9	232.7 ± 123.8	n.s.
p-Tau (pg/mL)	31.5 ± 18.2	31.4 ± 11.4	n.s.
α-syn (pg/mL)	896.8 ± 343.3	1164.2 ± 505.6 *(n = 37)*	**< 0.01**

Abbreviations: n = number; y = years; other abbreviations are spelled out in the text. **Statistically significant results are marked in bold**.

3.3. Multivariable linear regression analyses

We performed multivariable linear regression analyses to confirm the partial correlation findings, using serum HDL as the independent variable and clinical and biological markers as dependent variables. Age, sex, and *APOE* ε4 status were included as covariates in all models. The associations that emerged as significant in the partial correlation analyses remained statistically significant in the multivariable linear regression models, further supporting the robustness and consistency of these relationships. Results are presented in Supplementary Table 1.

4. Discussion

Serum lipid levels, specifically cholesterol and triglycerides, are well-known risk factors for vascular diseases. Recent evidence also suggests a potential role even in neurodegenerative disease, PD in particular (Hurh et al., 2022; Jiang et al., 2020; Kamano et al., 2024). However, the existing literature does not display univocal results, and direct investigations on the contribution of serum lipids to the biological profile of patients are still lacking.

In this study, we measured serum cholesterol and triglyceride levels in an early-stage PD population, stratified per *APOE* status, and examined correlations with clinical parameters and CSF biomarkers of neurodegeneration.

First, we did not observe differences in HDL, NonHDL, total cholesterol, and triglyceride serum levels between PD patients and controls. This finding is in line with other ones reported in previous studies (Hong et al., 2022; Hurh et al., 2022; Jiang et al., 2020), and probably derives from the inclusion/exclusion criteria of the study population that might have limited comorbidities.

Although in the absence of a significant case-control difference in serum lipid levels, we observed relevant associations between HDL and both clinical and biological markers of disease in PD. After adjusting for main confounding factors, serum HDL was inversely associated with motor symptom severity and directly associated with both CSF α-syn and amyloidopathy markers (Aβ42 and Aβ42/Aβ40). Specifically, lower HDL levels correlated with greater motor severity and a more unfavorable biomarker profile.

Additionally, given the known role of the *APOE* ε4 genotype in lipid metabolism and neurodegeneration (Huang and Mahley, 2014; Liampas et al., 2024; Piccarducci et al., 2023), we investigated whether the *APOE* genotype influenced these associations. While *APOE* ε4 carrier status had no significant impact on serum lipid levels, α-synuclein, or total tau, we found that *APOE* ε4 carriers had significantly higher CSF p-Tau and lower Aβ42/Aβ40 compared to non-carriers. These results align with previous literature associating *APOE* ε4 with increased amyloid deposition and tau pathology, predominantly reported in Alzheimer's disease but increasingly acknowledged as relevant in PD (Liampas et al., 2024; Michaelson, 2014; Rosal et al., 2025; Zenuni et al., 2023). Importantly, adjusting for *APOE* ε4 carrier status did not affect the strength or significance of the associations between HDL and clinical-biological parameters, suggesting that HDL's putative protective role may be independent of *APOE* genotype.

HDL is synthesized in the liver and intestines and transports cholesterol through the human body. Apolipoprotein A1 (ApoA1) is the major HDL protein component and can cross the blood-brain barrier (BBB), thus entering the CNS and impacting brain lipid homeostasis

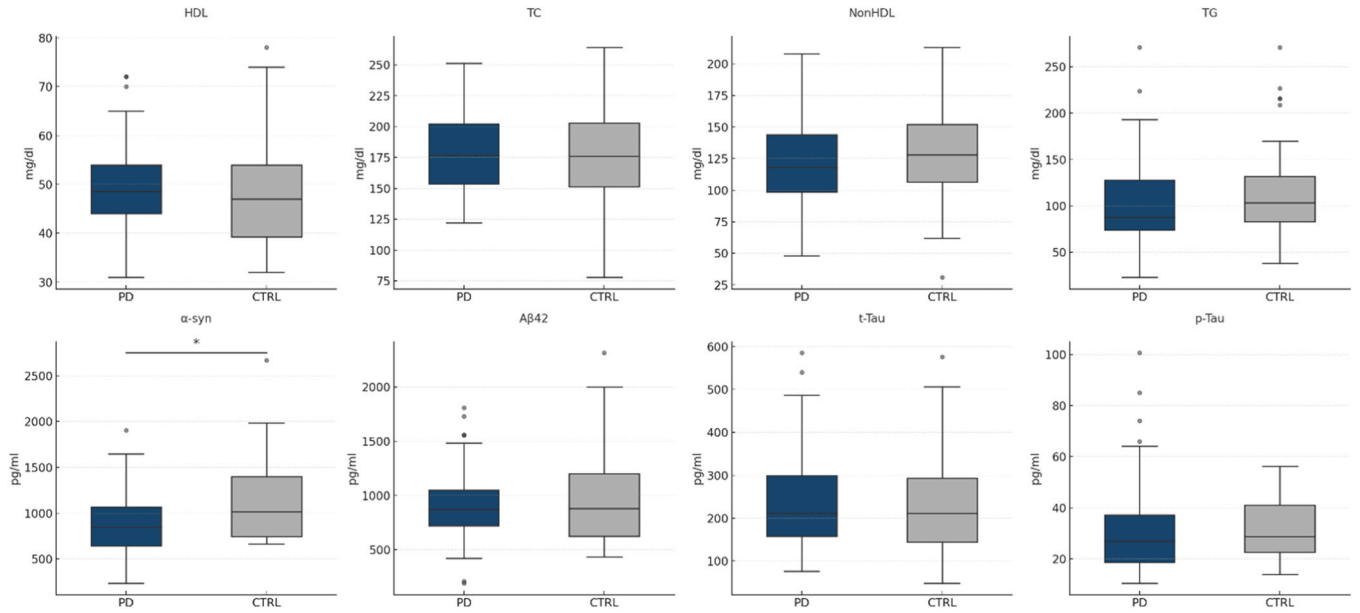

Fig. 1. Group comparisons of serum lipid levels and CSF biomarkers between PD and CTRL.Group comparisons of serum lipid levels (TC, HDL, NonHDL, TG) and CSF biomarkers (α-syn, Aβ42, t-Tau, p-Tau) between PD and CTRL. A significant reduction in CSF α-syn levels was observed in the PD group ($p < 0.01$), while no significant differences emerged for other parameters. Data are shown as boxplots; horizontal lines represent medians, boxes indicate interquartile ranges, and whiskers denote 1.5 × IQR. Dots represent outliers. * indicates $p < 0.05$.

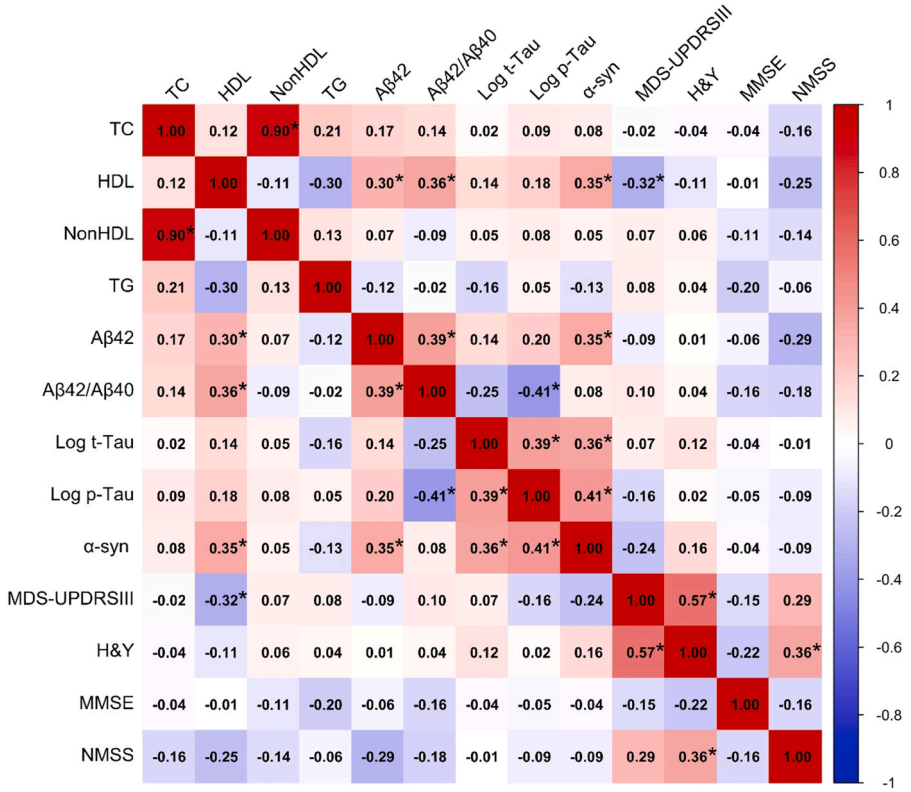

Fig. 2. The heatmap showing partial correlation coefficients between serum lipid levels, CSF biomarkers, and clinical parameters in Parkinson's disease patients, adjusted for age and sex. Positive correlations are shown in red, negative correlations in blue; color intensity reflects the strength of the association (see color bar). * indicate statistically significant correlations after false discovery rate (FDR) correction ($p < 0.05$).

(Mahley et al., 1984; van der Vorst, 2020). There is compelling evidence of the multiple roles of this apolipoprotein that may account for its possible involvement in neurodegenerative diseases, including PD (Emamzadeh, 2017). ApoA1 is critical in maintaining brain cholesterol homeostasis and regulating local and systemic inflammation, two main drivers of protein misfolding and aggregation (Frankel et al., 2023; Vitali et al., 2014). Specifically, in several experimental models, ApoA1 interfered with the amyloid-β (Aβ) fibrils formation and nucleation

processes, counteracting the occurrence of synucleinopathy and amyloidopathy, as well as promoting Aβ efflux across the BBB, reducing the Aβ aggregation (Emamzadeh, 2017; Frankel et al., 2023; Magro et al., 2019). In a few studies, the ApoA1 levels were found reduced either in CSF or serum of PD patients in association with an earlier disease onset and a more severe motor phenotype (Swanson et al., 2015), which supports the relevance of ApoA1 lowering to PD pathogenesis or the potential neuroprotection due to its higher levels (Paslawski and Svenningsson, 2023; Qiang et al., 2013; Wang et al., 2010). Finally, a recent work indicated that lipoprotein species can inhibit α-synuclein aggregation in the CSF (Bellomo et al., 2023).

Our findings thus agree with these data, showing how higher HDL circulating levels may reflect a milder clinical-biological PD profile, consistent with a possible neuroprotective effect. The positive correlation between HDL and α-syn may have different biological interpretations. In PD, the higher CSF α-syn levels could indicate reduced pathological aggregation within the brain in Lewy-type inclusions, reflecting a milder synuclein-related pathology (Barba et al., 2022; Majbour et al., 2016; Parnetti et al., 2019). In this scenario, HDL might aid in the clearance or stabilization of soluble α-syn, helping preserve synaptic integrity and limit the formation of toxic oligomers (Burré et al., 2015), ultimately resulting in milder clinical manifestations. Otherwise, we should acknowledge that, in other complex synucleinopathies with concurrent AD co-pathology, CSF α-syn levels can instead directly mirror widespread synaptic loss (Barba et al., 2023), basically accounting for a quite ambiguous interpretation of the total CSF α-syn levels.

Nevertheless, we cannot exclude that elevated HDL reflects better overall health and lower vascular burden, which might independently slow PD progression (Imbriani et al., 2020; Wei et al., 2023).

In contrast, NonHDL cholesterol fractions, such as low-density lipoproteins and very-low-density lipoproteins, are considered mild risk factors for the development of cognitive impairment in general; however, their relationships with neurodegenerative processes remain poorly defined (Poliakova and Wellington, 2023). This distinction may explain the lack of correlation between NonHDL cholesterol or TC levels and the clinical-biological profile of our early-stage PD cohort.

Despite the limitations due to the sample size, the absence of replication cohorts, the cross-sectional design, the limited neurodegeneration biomarker panel (e.g., absence of CSF ApoA-I or neurofilaments), and the lack of stratification for life habits (e.g., smoking, diet, physical exercise) (Beyene et al., 2020), this study demonstrated in vivo a direct correlation between the serum lipids and the clinical-biological profile of early-stage PD.

Although within a normal range, we showed that lower HDL levels may contribute to a worse disease presentation, independently of *APOE* genotype. Larger, multicenter studies including serum and CSF lipidomics, with longitudinal follow-up, are now needed to confirm these observations and support the development of novel therapeutic strategies targeting lipid metabolism through lifestyle and dietary interventions readily applicable in clinical practice.

Disclosure

All authors disclose:

- There are no actual or potential conflicts of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the work submitted that could inappropriately influence (bias) this work.
- There are no contracts relating to this research through which it any organization may stand to gain financially now or in the future.
- There are no financial interest in this work.
- There are no sources of financial support related to the manuscript being submitted.
- All the data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.
- Appropriate approval and procedures were used concerning human subjects
- All authors have reviewed the contents of the manuscript being submitted, approve of its contents and validate the accuracy of the data.

CRediT authorship contribution statement

Silvio Bagetta: Data curation. **Giulia Maria Sancesario:** Validation. **Veronica Buttarazzi:** Data curation. **Maria Mancini:** Data curation. **Tommaso Schirinzi:** Writing – review & editing, Supervision, Methodology. **Roberta Bovenzi:** Data curation. **Enrica Marchionni:** Supervision, Writing – original draft. **Clara Simonetta:** Data curation. **Alessandro Stefani:** Writing – review & editing, Supervision. **Nicola Biagio Mercuri:** Supervision. **Jacopo Bissacco:** Data curation. **Federica Veltri:** Methodology. **Davide Mascioli:** Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Matteo Conti:** Software, Methodology, Formal analysis. **Daniela Maftei:** Methodology. **Massimo Pieri:** Writing – original draft, Supervision.

Ethical approval

The study was approved by the local ethics committee (protocol n° 16.21) and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

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Declaration of Competing Interest

The authors have no relevant financial or non-financial interests to disclose.

Acknowledgment

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2025.07.004.

Data availability

The datasets generated during the current study are available from the corresponding author on reasonable request.

References

Alecu, I., Bennett, S.A.L., 2019. Dysregulated lipid metabolism and its role in α-synucleinopathy in Parkinson's disease. Front. Neurosci. https://doi.org/10.3389/fnins.2019.00328.

Barba, L., Abu-Rumeileh, S., Barthel, H., Massa, F., Foschi, M., Bellomo, G., Gaetani, L., Thal, D.R., Parnetti, L., Otto, M., 2024. Clinical and diagnostic implications of Alzheimer's disease copathology in Lewy body disease. Brain 147, 3325–3343. https://doi.org/10.1093/brain/awae203.

Barba, L., Abu-Rumeileh, S., Halbgebauer, S., Bellomo, G., Paolini Paoletti, F., Gaetani, L., Oeckl, P., Steinacker, P., Massa, F., Parnetti, L., Otto, M., 2023. CSF synaptic biomarkers in AT(N)-based subgroups of lewy body disease. Neurology 101, E50–E62. https://doi.org/10.1212/WNL.0000000000207371.

Barba, L., Paolini Paoletti, F., Bellomo, G., Gaetani, L., Halbgebauer, S., Oeckl, P., Otto, M., Parnetti, L., 2022. Alpha and beta synucleins: from pathophysiology to clinical application as biomarkers. Mov. Disord. 37, 669–683. https://doi.org/10.1002/mds.28941.

Bellomo, G., Paciotti, S., Concha-Marambio, L., Rizzo, D., Wojdała, A.L., Chiasserini, D., Gatticchi, L., Cerofolini, L., Giuntini, S., De Luca, C.M.G., Ma, Y., Farris, C.M., Pieraccini, G., Bologna, S., Filidei, M., Ravera, E., Lelli, M., Moda, F., Fragai, M., Parnetti, L., Luchinat, C., 2023. Cerebrospinal fluid lipoproteins inhibit α-synuclein aggregation by interacting with oligomeric species in seed amplification assays. Mol. Neurodegener. 18. https://doi.org/10.1186/s13024-023-00613-8.

Beyene, H.B., Olshansky, G., Smith, A.A.T., Giles, C., Huynh, K., Cinel, M., Mellett, N.A., Cadby, G., Hung, J., Hui, J., Beilby, J., Watts, G.F., Shaw, J.S., Moses, E.K., Magliano, D.J., Meikle, P.J., 2020. High-coverage plasma lipidomics reveals novel sex-specific lipidomic fingerprints of age and BMI: evidence from two large population cohort studies. PLoS Biol. 18. https://doi.org/10.1371/journal.pbio.3000870.

Blaha, M.J., Blumenthal, R.S., Brinton, E.A., Jacobson, T.A., 2008. The importance of non-HDL cholesterol reporting in lipid management. J. Clin. Lipido. https://doi.org/10.1016/j.jacl.2008.06.013.

Burré J, Sharma M, Südhof TC. Definition of a molecular pathway mediating α-synuclein neurotoxicity. *J Neurosci.* 2015 Apr 1;35(13):5221-32. doi: 10.1523/JNEUROSCI.4650-14.2015. Erratum in: *J Neurosci.* 2024 May 22;44(21):e0790242024. doi: 10.1523/JNEUROSCI.0790-24.2024. PMID: 25834048; PMCID: PMC4380997.

Dai, L., Zou, L., Meng, L., Qiang, G., Yan, M., Zhang, Z., 2021. Cholesterol metabolism in neurodegenerative diseases: molecular mechanisms and therapeutic targets. Mol. Neurobiol. 58, 2183–2201. https://doi.org/10.1007/S12035-020-02232-6.

van der Vorst, E.P.C., 2020. High-density lipoproteins and apolipoprotein A1. Subcell Biochem. 399–420. https://doi.org/10.1007/978-3-030-41769-7_16.

Emamzadeh, F.N., 2017. Role of apolipoproteins and α-synuclein in Parkinson's Disease. J. Mol. Neurosci. https://doi.org/10.1007/s12031-017-0942-9.

Frankel, R., Sparr, E., Linse, S., 2023. Retardation of Aβ42 fibril formation by apolipoprotein A-I and recombinant HDL particles. J. Biol. Chem. 299. https://doi.org/10.1016/j.jbc.2023.105273.

Gordon, S.M., Hofmann, S., Askew, D.S., Davidson, W.S., 2011. High density lipoprotein: it's not just about lipid transport anymore. Trends Endocrinol. Metab. 22, 9. https://doi.org/10.1016/J.TEM.2010.10.001.

Gu, L., Shu, H., Wang, Y., Li, H., Wang, P., 2024. Association of lipid levels with motor and cognitive function and decline in Parkinson's disease. Psychogeriatrics 24, 802–810. https://doi.org/10.1111/psyg.13122.

Hayes, M.T., 2019. Parkinson's disease and Parkinsonism. Am. J. Med. 132, 802–807. https://doi.org/10.1016/j.amjmed.2019.03.001.

Hong, X., Guo, W., Li, S., 2022. Lower blood lipid level is associated with the occurrence of Parkinson's disease: a meta-analysis and systematic review. Int. J. Clin. Pr. 2022. https://doi.org/10.1155/2022/9773038.

Huang, Y., Mahley, R.W., 2014. Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. Neurobiol. Dis. https://doi.org/10.1016/j.nbd.2014.08.025.

Hurh, K., Park, M., Jang, S. in, Park, E.C., Jang, S.Y., 2022. Association between serum lipid levels over time and risk of Parkinson's disease. Sci. Rep. 12, 1–9. https://doi.org/10.1038/s41598-022-25180-8.

Imbriani, P., D'Angelo, V., Platania, P., Di Lazzaro, G., Scalise, S., Salimei, C., El Atiallah, I., Colona, V.L., Mercuri, N.B., Bonsi, P., Pisani, A., Schirinzi, T., Martella, G., 2020. Ischemic injury precipitates neuronal vulnerability in Parkinson's disease: insights from PINK1 mouse model study and clinical retrospective data. Park. Relat. Disord. 74, 57–63. https://doi.org/10.1016/j.parkreldis.2020.04.004.

Jack, C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., Holtzman, D.M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J.L., Montine, T., Phelps, C., Rankin, K.P., Rowe, C.C., Scheltens, P., Siemers, E., Snyder, H.M., Sperling, R., Elliott, C., Masliah, E., Ryan, L., Silverberg, N., 2018. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimer'S. Dement. https://doi.org/10.1016/j.jalz.2018.02.018.

Jeong, S.H., Lee, H.S., Chung, S.J., Yoo, H.S., Jung, J.H., Baik, K., Baik, J.S., Sohn, Y.H., Lee, P.H., 2023. Association of cholesterol level with dopamine loss and motor deficits in Parkinson disease: a cross-sectional study. Eur. J. Neurol. 30, 107–115. https://doi.org/10.1111/ene.15592.

Jiang, Z., Xu, X., Gu, X., Ou, R., Luo, X., Shang, H., Song, W., 2020. Effects of higher serum lipid levels on the risk of parkinson's disease: a systematic review and meta-analysis. Front. Neurol. https://doi.org/10.3389/fneur.2020.00597.

Kamano, S., Ozawa, D., Ikenaka, K., Nagai, Y., 2024. Role of lipids in the pathogenesis of Parkinson's disease. Int. J. Mol. Sci. https://doi.org/10.3390/ijms25168935.

Liampas, I., Kyriakoulopoulou, P., Siokas, V., Tsiamaki, E., Stamati, P., Kefalopoulou, Z., Chroni, E., Dardiotis, E., 2024. Apolipoprotein E gene in α-synucleinopathies: a narrative review. Int. J. Mol. Sci. https://doi.org/10.3390/ijms25031795.

Liddle, R.A., 2018. Parkinson's disease from the gut. Brain Res. 1693, 201–206. https://doi.org/10.1016/j.brainres.2018.01.010.

Liu, C.-C., Kanekiyo, T., Xu, H., Bu, G., 2013a. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat. Rev. Neurol. 9, 106–118. https://doi.org/10.1038/nrneurol.2012.263.

Liu, C.-C., Kanekiyo, T., Xu, H., Bu, G., 2013b. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat. Rev. Neurol. 9, 106–118. https://doi.org/10.1038/nrneurol.2012.263.

Lu, Y., Jin, X., Zhao, P., 2021. Serum lipids and the pathogenesis of Parkinson's disease: a systematic review and meta-analysis. Int. J. Clin. Pr. 75. https://doi.org/10.1111/IJCP.13865.

Magro, R.D., Simonelli, S., Cox, A., Formicola, B., Corti, R., Cassina, V., Nardo, L., Mantegazza, F., Salerno, D., Grasso, G., Deriu, M.A., Danani, A., Calabresi, L., Re, F., 2019. The extent of human apolipoprotein a-i lipidation strongly affects the β-amyloid efflux across the blood-brain barrier in vitro. Front. Neurosci. 13. https://doi.org/10.3389/fnins.2019.00419.

Mahley, R.W., Innerarity, T.L., Rall, S.C., Weisgraber, K.H., 1984. Plasma lipoproteins: Apolipoprotein structure and function. J Lipid Res. https://doi.org/10.1016/s0022-2275(20)34443-6.

Majbour, N.K., Vaikath, N.N., Eusebi, P., Chiasserini, D., Ardah, M., Varghese, S., Haque, M.E., Tokuda, T., Auinger, P., Calabresi, P., Parnetti, L., El-Agnaf, O.M.A., 2016. Longitudinal changes in CSF alpha-synuclein species reflect Parkinson's disease progression. Mov. Disord. 31, 1535–1542. https://doi.org/10.1002/mds.26754.

Michaelson, D.M., 2014. APOE ε4: The most prevalent yet understudied risk factor for Alzheimer's disease. Alzheimer's Dement. https://doi.org/10.1016/j.jalz.2014.06.015.

Nakamura, A., Kaneko, N., Villemagne, V.L., Kato, T., Doecke, J., Doré, V., Fowler, C., Li, Q.X., Martins, R., Rowe, C., Tomita, T., Matsuzaki, K., Ishii, Kenji, Ishii, Kazunari, Arahata, Y., Iwamoto, S., Ito, K., Tanaka, K., Masters, C.L., Yanagisawa, K., 2018. High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature 554, 249–254. https://doi.org/10.1038/nature25456.

Parnetti, L., Gaetani, L., Eusebi, P., Paciotti, S., Hansson, O., El-Agnaf, O., Mollenhauer, B., Blennow, K., Calabresi, P., 2019. CSF and blood biomarkers for Parkinson's disease. Lancet Neurol. 18, 573–586. https://doi.org/10.1016/S1474-4422(19)30024-9.

Paslawski, W., Svenningsson, P., 2023. Elevated ApoE, ApoJ and lipoprotein-bound α-synuclein levels in cerebrospinal fluid from Parkinson's disease patients – validation in the BioFIND cohort. Park. Relat. Disord. 116. https://doi.org/10.1016/j.parkreldis.2023.105765.

Piccarducci, R., Giacomelli, C., Bertilacchi, M.S., Benito-Martinez, A., Di Giorgi, N., Daniele, S., Signore, G., Rocchiccioli, S., Vilar, M., Marchetti, L., Martini, C., 2023. Apolipoprotein E ε4 triggers neurotoxicity via cholesterol accumulation, acetylcholine dyshomeostasis, and PKCε mislocalization in cholinergic neuronal cells. Biochim. Et. Biophys. Acta Mol. Basis Dis. 1869, 166793. https://doi.org/10.1016/j.bbadis.2023.166793.

Poliakova, T., Wellington, C.L., 2023. Roles of peripheral lipoproteins and cholesteryl ester transfer protein in the vascular contributions to cognitive impairment and dementia. Mol. Neurodegener. https://doi.org/10.1186/s13024-023-00671-y.

Postuma, R.B., Berg, D., Stern, M., Poewe, W., Olanow, C.W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A.E., Halliday, G., Goetz, C.G., Gasser, T., Dubois, B., Chan, P., Bloem, B.R., Adler, C.H., Deuschl, G., 2015. MDS clinical diagnostic criteria for Parkinson's disease. Mov. Disord. https://doi.org/10.1002/mds.26424.

Pu, J.L., Jin, C.Y., Wang, Z.X., Fang, Y., Li, Y.L., Xue, N.J., Zheng, R., Lin, Z.H., Yan, Y.Q., Si, X.L., Chen, Y., Liu, Y., Song, Z., Yan, Y.P., Tian, J., Yin, X.Z., Zhang, B.R., 2022. Apolipoprotein E genotype contributes to motor progression in Parkinson's disease. Mov. Disord. 37, 196–200. https://doi.org/10.1002/mds.28805.

Qiang, J.K., Wong, Y.C., Siderowf, A., Hurtig, H.I., Xie, S.X., Lee, V.M.Y., Trojanowski, J. Q., Yearout, D., Leverenz, B., Montine, J., Stern, T.J., Mendick, M., Jennings, S., Zabetian, D., Marek, C., Chen-Plotkin, K., A.S, 2013. Plasma apolipoprotein A1 as a biomarker for Parkinson disease. Ann. Neurol. 74, 119–127. https://doi.org/10.1002/ana.23872.

Rosal, A.E., Martin, S.L., Strafella, A.P., 2025. The role of apolipoprotein E4 on cognitive impairment in Parkinson's disease and Parkinsonisms. Front Neurosci. 19. https://doi.org/10.3389/fnins.2025.1515374.

Sancesario, G.M., Di Lazzaro, G., Alwardat, M., Biticchi, B., Basile, V., Salimei, C., Colona, V.L., Sinibaldi Salimei, P., Bernardini, S., Mercuri, N.B., Pisani, A., Schirinzi, T., 2020. Amyloid-β42/neurogranin ratio as a potential index for cognitive impairment in Parkinson's disease. J. Alzheimer's Dis. 76, 1171–1178. https://doi.org/10.3233/JAD-200344.

Schirinzi, T., Sancesario, G.M., Di Lazzaro, G., Biticchi, B., Colona, V.L., Mercuri, N.B., Bernardini, S., Pisani, A., 2019. CSF α-synuclein inversely correlates with non-motor symptoms in a cohort of PD patients. Park. Relat. Disord. 61, 203–206. https://doi.org/10.1016/j.parkreldis.2018.10.018.

Swanson, C.R., Berlyand, Y., Xie, S.X., Alcalay, R.N., Chahine, L.M., Chen-Plotkin, A.S., 2015. Plasma apolipoprotein A1 associates with age at onset and motor severity in early Parkinson's disease patients. Mov. Disord. 30, 1648–1656. https://doi.org/10.1002/mds.26290.

Tansey, M.G., Wallings, R.L., Houser, M.C., Herrick, M.K., Keating, C.E., Joers, V., 2022. Inflammation and immune dysfunction in Parkinson disease. Nat. Rev. Immunol. 22, 657–673. https://doi.org/10.1038/s41577-022-00684-6.

Tomlinson, C.L., Stowe, R., Patel, S., Rick, C., Gray, R., Clarke, C.E., 2010. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov. Disord. 25, 2649–2653. https://doi.org/10.1002/mds.23429.

Vitali, C., Wellington, C., Calabresi, L., Paoletti, F.G., 2014. HDL and cholesterol handling in the brain. Downloaded.

Wang, E.S., Sun, Y., Guo, J.G., Gao, X., Hu, J.W., Zhou, L., Hu, J., Jiang, C.C., 2010. Tetranectin and apolipoprotein A-I in cerebrospinal fluid as potential biomarkers for Parkinson's disease. Acta Neurol. Scand. 122 350359. https://doi.org/10.1111/j.1600-0404.2009.01318.x.

Wei, J., Wong, L.C., Boland, S., 2023. Lipids as emerging biomarkers in neurodegenerative diseases. Int. J. Mol. Sci. 25. https://doi.org/10.3390/IJMS25010131.

Yacoubian, T.A., Fang, Y.H.D., Gerstenecker, A., Amara, A., Stover, N., Ruffrage, L., Collette, C., Kennedy, R., Zhang, Y., Hong, H., Qin, H., McConathy, J., Benveniste, E. N., Standaert, D.G., 2023. Brain and systemic inflammation in De Novo Parkinson's disease. Mov. Disord. 38, 743–754. https://doi.org/10.1002/mds.29363.

Yang, W., Chang, Z., Que, R., Weng, G., Deng, B., Wang, T., Huang, Z., Xie, F., Wei, X., Yang, Q., Li, M., Ma, K., Zhou, F., Tang, B., Mok, V.C.T., Zhu, S., Wang, Q., 2020. Contra-directional expression of plasma superoxide dismutase with lipoprotein cholesterol and high-sensitivity C-reactive protein as important markers of Parkinson's Disease severity. Front. Aging Neurosci. 12. https://doi.org/10.3389/fnagi.2020.00053.

Yang, L.G., March, Z.M., Stephenson, R.A., Narayan, P.S., 2023. Apolipoprotein E in lipid metabolism and neurodegenerative disease. Trends Endocrinol. Metab. 34, 430–445. https://doi.org/10.1016/j.tem.2023.05.002.

Yoon, J.H., Seo, Y., Jo, Y.S., Lee, S., Cho, E., Cazenave-Gassiot, A., Shin, Y.-S., Moon, M. H., An, H.J., Wenk, M.R., Suh, P.-G., 2022. Brain lipidomics: from functional landscape to clinical significance. Sci. Adv. 8. https://doi.org/10.1126/sciadv.adc9317.

Zenuni, H., Bovenzi, R., Bissacco, J., Grillo, P., Simonetta, C., Mascioli, D., Pieri, M., Bernardini, S., Sancesario, G.M., Stefani, A., Mercuri, N.B., Schirinzi, T., 2023. Clinical and neurochemical correlates of the APOE genotype in early-stage Parkinson's disease. Neurobiol. Aging 131, 24–28. https://doi.org/10.1016/j.neurobiolaging.2023.07.011.