

# HDL CHOLESTEROL IS INDEPENDENTLY ASSOCIATED WITH COGNITIVE FUNCTION IN MALES BUT NOT IN FEMALES WITHIN A COHORT OF NONAGENARIANS: THE MUGELLO STUDY

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**Abstract:** *Objectives:* To investigate the possible relationship between lipid profile and cognitive functions in a cohort of nonagenarians enrolled within the Mugello Study, an epidemiological study aimed at investigating both clinically relevant geriatric items and various health issues. *Design:* Cross-sectional survey. *Setting:* This study focused on oldest old community-dwelling participants. *Participants:* Three hundred twenty-five nonagenarians (218 F, median age: 92 years). *Measurements:* Participants were evaluated through laboratory, instrumental examinations and questionnaires concerning lifestyle, dietary habits and cognitive status. *Results:* Females are older, with a lower level of education, live more prevalently on their own and have higher values for total cholesterol and high-density lipoprotein cholesterol (HDL) compared to males. With regard to functional and cognitive measures females report a significantly lower skill level in the physical activity performance, with a level of independence that is better for both basic and instrumental activities. In order to investigate whether there was an association between lipid variables and cognitive function as measured by the Mini-Mental State Examination a multiple regression analysis was performed with adjustments for confounding variables based on gender. In males, HDL cholesterol showed a significant relationship with Mini-Mental State Examination after a complete adjustment with years of education, physical activity performance and daily living activities ( $\beta = 0.174$ ;  $p=0.037$ ). In females HDL cholesterol showed a significant association only in the model adjusted for age and body mass index, losing its associations as soon as the cohabitation state and the depression status entered the model. *Conclusion:* Our results support the hypothesis that HDL cholesterol is significantly linked to cognitive functions, especially in males of a cohort of very old people.

**Key words:** Lipid, cholesterol, dementia, elderly.

**Abbreviations:** HDL: High-density lipoprotein cholesterol; BADL: Basic Activities of Daily Living; IADL: Instrumental Activities of Daily Living; SPPB: Short Physical Performance Battery; MMSE: Mini-Mental State Examination.

## Introduction

Dementia is characterized by progressive deterioration of cognitive functions which eventually leads to loss of independence (1). As the most important risk factor for dementia is old age, the prevalence of dementia is increasing with the aging of populations all over the world (2). There is currently no effective treatment for dementia, so research in the area of cognitive impairment focuses on the possible predictors of this disorder. Vascular risk factors have been considered since cerebrovascular disease is an important contribution to dementia (3), and in particular lipid variables have been widely explored in this context. Reports in the literature concerning the association between lipid concentrations and risk of dementia have shown inconsistent results. On the one hand, some studies have suggested that total cholesterol and/or lipoproteins levels in middle age may represent a potential risk factor for the subsequent onset of cognitive impairment and Alzheimer's disease in old age (4, 5). On the other hand, it has been reported that low levels of total cholesterol in old age (65 years and

over) may be cognitively detrimental in the absence of other cardiovascular risk factors, as they have been associated with worse performance on memory and speed measurements (6) and with a higher risk of developing dementia and Alzheimer's disease (7, 8). This is especially true with regard to very old people (90 years and over), who represent the fastest growing segment of the elderly population in all high-income countries (9) and whose peculiar health hinders the generalization of epidemiological results of individuals aged 65-90 years. Data on this segment of the population are still few and inconsistent (10-12). The aim of the present study is to analyse the possible relationship between lipid profile and cognitive functions in a sample of very old people, taken in the context of an epidemiological study, the Mugello Study.

## Material and Methods

### Study population

This study is based on the data of the Mugello Study, a cross-sectional survey of people aged 90 years and more, living

in the Mugello area (north-east of Florence, Tuscany, Italy). The study protocol has been described in detail elsewhere (13). Data on the study sample were collected at the homes/retirement homes through objective examinations and questionnaires. In cases where the respondent was cognitively impaired, or otherwise too incapable of being interviewed, a delegate was interviewed instead. Information on demographic data, education, functional and cognitive status, medical history and drug use was collected and blood sample was taken from each participant. Informed written consent was obtained from all participants, or their delegates, to be included in the study and subjected to blood sampling. The protocol of the Mugello study was in accordance with the principles of the Declaration of Helsinki on clinical research involving human beings and was approved by the Ethical Committee of the Don Gnocchi Foundation. Among the 504 subjects enrolled in the Mugello study, 117 subjects were excluded due to severe hearing loss, blindness or because they refused to provide blood samples. The final sample consisted of 387 subjects, 107 men and 280 women.

#### **Outcome measures**

All subjects were instructed to fast for 12 hours before blood withdrawal. Blood samples were analysed through conventional procedures. Depressive symptoms were assessed using the 15-item Geriatric Depression Scale. Subjects were categorized into depressed and non-depressed using a cut-off of 12 or greater (14). The level of independence in performing daily activities was measured using the Basic Activities of Daily Living (BADL) (15) and the Instrumental Activities of Daily Living (IADL) tools (16). The BADL tool was used to evaluate the ability to bathe, dress, use the bathroom, get in and out of bed, defecate, and eat, with a total score ranging from 0 (complete independence) to 6 (complete dependence). The IADL tool was used to evaluate the ability to use the phone, go shopping, prepare meals, do housework, do laundry, travel, take medicine, and manage finances, with a total score ranging from 0 (complete independence) to 8 (complete dependence). Physical performance was assessed using the Short Physical Performance Battery (SPPB) (17) which evaluates walking speed, standing balance and the ability to stand up from a chair. The total score varies between 0 and 12, with a higher score indicating a better performance. Global cognitive function was evaluated with the Mini-Mental State Examination (MMSE) [18]. The global score ranges between 0 and 30, with a lower score indicating a more severe impairment. Since the score correction for nonagenarians is not available in the literature, the raw MMSE score was used in this analysis.

#### **Statistical analysis**

Statistical analysis was performed using SPSS 24.0 software (IBM SPSS, Chicago, Illinois, USA). First, data were checked for normality using the Shapiro-Wilk test. Prior to entry into the analysis, age and years of education were

log-transformed to obtain a normal distribution, while the triglyceride level was transformed with a square root, for the same purpose. The relationship between MMSE score and variables that describe anthropometric and sociodemographic characteristics, the presence of comorbidity, drug use, physical performance and level of independence was studied using linear regression analysis. The variables showing a statistically significant association with MMSE were introduced as potential confounding factors in a multiple linear regression model, to study the possible association between cognitive function and lipid concentration levels. Three models were built for this purpose. In Model 1, lipid variables that showed a significant relation at the univariate analysis were adjusted only for age, and body mass index (BMI). In Model 2, years of education, cohabitation, and depression have been added as confounding factors. Model 3 has been adapted for Model 2 and for comorbidities, drugs and for variables related to physical performance and level of independence. In all analyses, a  $p$ -value  $< 0.05$  was considered statistically significant.

#### **Results**

The study population comprised 107 males and 218 females with a median age of 92 years. The baseline demographic and clinical characteristics of the study population by gender are reported in Table 1. Females are older, with a lower level of education, live more prevalently on their own and have higher values for total cholesterol and HDL cholesterol compared to males. With regard to functional and cognitive measures females report a significantly lower skill level in the physical activity performance, with a level of independence that is better for both basic and instrumental activities. MMSE is significantly higher in males than females.

To evaluate the possible relationship between the evaluation of cognitive function by MMSE and demographic, clinical, and lipid parameters a linear regression analysis was performed separately in males and females (Table 2). In males, years of education and physical activity performance were significantly and positively associated with MMSE, while both basic and instrumental activities showed significant negative association with MMSE. With regard to lipid variables, total cholesterol and HDL cholesterol were significantly and positively associated with MMSE. In females, BMI, the presence of cardiovascular disease and physical activity performance showed a significant positive correlation with MMSE, while the cohabitation status, depression, the use of antipsychotics and the basic and instrumental activities reported a significant negative relationship. Regarding the lipid variables, also in this case the total cholesterol and HDL cholesterol were significantly and positively correlated with MMSE.

In an attempt to investigate whether there was an association between lipid variables and MMSE a multiple regression analysis was performed with adjustments for confounding variables based on gender. In males (Table 3), total cholesterol

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lost its significant association with MMSE when only age was included in the model, while HDL cholesterol showed a significant relationship with MMSE also after a complete adjustment with years of education, physical activity performance and daily living activities ( $\beta = 0.174$ ;  $p=0.037$ ).

**Table 1**

Baseline demographic and clinical characteristics of the study population

|                                     | Males (n=107) | Females (n=280) | p value |
|-------------------------------------|---------------|-----------------|---------|
| Age, years*                         | 91 [4.0]      | 92 [4.0]        | 0.010   |
| BMI, kg/m <sup>2</sup> <sup>a</sup> | 25.1±3.5      | 25.1±5.0        | 0.963   |
| Education, (years)*                 | 5 [2.0]       | 3 [2.0]         | <0.001  |
| Cohabitation status                 |               |                 |         |
| Alone, n (%)                        | 13 (12.9%)    | 60 (24.4%)      |         |
| With relatives, n (%)               | 81 (80.2%)    | 159 (64.6%)     | 0.016   |
| With non-relatives, n (%)           | 7 (6.9%)      | 27 (11.0%)      |         |
| Comorbidity                         |               |                 |         |
| Depression, n (%)                   | 7 (7.4%)      | 27 (12.6%)      | 0.178   |
| Cancer, n (%)                       | 13 (12.1%)    | 31 (11.2%)      | 0.783   |
| Cerebrovascular disease, n (%)      | 21 (19.6%)    | 61 (21.6%)      | 0.619   |
| Cardiovascular disease, n (%)       | 43 (40.2%)    | 134 (47.9%)     | 0.176   |
| Diabetes, n (%)                     | 11 (10.3%)    | 42 (15.1%)      | 0.218   |
| Drugs                               |               |                 |         |
| Benzodiazepines, n (%)              | 16 (15%)      | 47 (16.9%)      | 0.643   |
| Antidepressants, n (%)              | 17 (15.9%)    | 57 (20.5%)      | 0.303   |
| Antipsychotics, n (%)               | 7 (6.5%)      | 34 (12.2%)      | 0.105   |
| Lipid-lowering drugs, n (%)         | 12 (11.2%)    | 20 (7.2%)       | 0.200   |
| Functional and cognitive measures   |               |                 |         |
| SPPB                                | 4.4±3.8       | 2.7±3.0         | <0.001  |
| BADL                                | 2.3±1.5       | 2.6±1.7         | 0.097   |
| IADL                                | 3.6±3.6       | 5.0±3.6         | <0.001  |
| MMSE                                | 22.4±8.2      | 18.4±9.3        | <0.001  |
| Lipid variables                     |               |                 |         |
| Total cholesterol, mg/dl            | 177.4±38.3    | 196.6±41.1      | <0.0001 |
| HDL cholesterol, mg/dl              | 52.4±13.5     | 60.0±17.7       | <0.001  |
| Triglycerides, mg/dl*               | 102.5 [54.75] | 102.5 [63.25]   | 0.387   |

\*Median [IQR]; All the other data are presented as mean ± SD; BMI = Body Mass Index; SPPB = Short Physical Performance Battery; BADL = Basic Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MMSE = Mini Mental State Examination

In females (Table 4), total cholesterol lost its significant association as soon as age and BMI entered the model while HDL cholesterol showed a significant association only in the model 1 adjusted for age and BMI, losing its associations as soon as the cohabitation state and the depression status entered the model (model 2). The fully adjusted model, adjusted for demographic characteristics, comorbidities, medications as well as physical activity performance and independence level has shown significant association with MMSE only for age and

instrumental activities of daily life.

**Discussion**

The present manuscript examined the possible relationship between lipid variables and cognitive measures in a large cohort of very old people taken from a population-based study, the Mugello Study. The main result is that HDL cholesterol was significantly associated with a better cognitive state, measured by the MMSE, but only in males and not in females where the association lost its significant association in a fully adjusted model. These results could probably help to better understand the physiological predictors of a successful living in such a particular cohort of very old subjects.

The relationship between lipid parameters and cognitive function has been studied with interest in the last decades, without obtaining univocal results (10-12). Some studies reported a significant positive association between total cholesterol and cognitive function (4, 5) whereas other found that low levels of total cholesterol can be detrimental for cognitive functions (6). Regarding HDL cholesterol, some studies of HDL and cognitive function suggested a null association (12), while others reported that HDL cholesterol was positively associated with multiple measures of cognitive performance (10, 11). In our study population, a particular cohort of nonagenarians, we were able to find a direct relationship between HDL cholesterol and MMSE. This finding is in line with other studies conducted in similar cohorts of very old people, such as the paper by Cheung et al. (10) which reported a positive association between high levels of HDL cholesterol and a successful aging measured by a cumulative aging index based on the performance of participants in various dimensions, including psychological well-being and cognition in a sample of 120 subjects aged 95 to 108 years, and the study by Atzmon et al. (11) which found that plasma HDL cholesterol levels were positively and significantly related with improved cognitive functions assessed by the MMSE in a cross-sectional study involving 139 subjects with an age range of 95 to 107 years. In contrast with the results of the present and previous studies, on the other hand, Dong et al., in a cohort of 709 very old subjects (aged 90 to 108 years), found no causal association between risk for cognitive impairment and total cholesterol, triglycerides, and HDL cholesterol (12).

The positive relationship between HDL and cognitive function is consistent with the mechanisms that link lipids to cerebral and cerebrovascular diseases. HDL cholesterol is used to remove excess cholesterol from cells and transport it to the liver through bile, thus preventing atherosclerosis and protecting the arteries. The low levels of HDL have been associated with decreased volume of the hippocampus, a particularly vulnerable area of the brain associated with neurodegenerative diseases (19). Given the positive association between HDL and the cardiovascular system, it seems highly plausible that higher levels of HDL can positively affect global

**Table 2**  
Linear regression analysis of the association between demographic, clinical and functional parameters and MMSE

|                          | Males (n=107)  |                                  |         | Females (n=208) |                                  |         |
|--------------------------|----------------|----------------------------------|---------|-----------------|----------------------------------|---------|
|                          | R <sup>2</sup> | Standardized Coefficients (Beta) | p value | R <sup>2</sup>  | Standardized Coefficients (Beta) | p value |
| Age, years               | 0.079          | -0.281                           | 0.003   |                 |                                  |         |
| BMI, kg/m <sup>2</sup>   | 0.115          | -0.086                           | 0.369   | 0.123           | 0.175                            | 0.003   |
| Education, years         | 0.217          | 0.310                            | 0.001   | 0.106           | 0.088                            | 0.146   |
| Cohabitation status      | 0.186          | -0.134                           | 0.146   | 0.203           | -0.343                           | <0.001  |
| Depression               | 0.048          | -0.177                           | 0.085   | 0.189           | -0.177                           | 0.005   |
| Cancer                   | 0.131          | 0.080                            | 0.386   | 0.100           | 0.055                            | 0.335   |
| Cerebrovascular disease  | 0.127          | 0.046                            | 0.618   | 0.108           | -0.104                           | 0.068   |
| Cardiovascular disease   | 0.135          | 0.099                            | 0.279   | 0.119           | 0.141                            | 0.013   |
| Diabetes                 | 0.126          | 0.038                            | 0.683   | 0.101           | -0.058                           | 0.313   |
| Benzodiazepines          | 0.125          | -0.023                           | 0.802   | 0.097           | 0.010                            | 0.864   |
| Antidepressants          | 0.125          | 0.015                            | 0.868   | 0.102           | -0.072                           | 0.212   |
| Antipsychotics           | 0.125          | -0.023                           | 0.806   | 0.193           | -0.310                           | <0.001  |
| Lipid-lowering drugs     | 0.125          | 0.012                            | 0.897   | 0.103           | 0.075                            | 0.193   |
| SPPB                     | 0.246          | 0.369                            | <0.001  | 0.310           | 0.475                            | <0.001  |
| BADL                     | 0.442          | -0.588                           | <0.001  | 0.413           | -0.603                           | <0.001  |
| IADL                     | 0.296          | -0.453                           | <0.001  | 0.374           | -0.543                           | <0.001  |
| Total cholesterol, mg/dl | 0.036          | 0.191                            | 0.049   | 0.075           | 0.274                            | <0.0001 |
| HDL cholesterol, mg/dl   | 0.115          | 0.339                            | <0.0001 | 0.076           | 0.276                            | <0.0001 |
| Triglycerides, mg/dl     | 0.002          | -0.042                           | 0.669   | 0.008           | 0.091                            | 0.128   |

BMI = Body Mass Index; SPPB = Short Physical Performance Battery; BADL = Basic Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MMSE = Mini Mental State Examination

**Table 3**  
Multiple linear regression analysis of the association between demographic, clinical and functional parameters and MMSE in males (n=107)

| Dependent variable: MMSE score | R <sup>2</sup> | β      | SE    | Std β  | p value |
|--------------------------------|----------------|--------|-------|--------|---------|
| Model 1                        | 0.222          |        |       |        |         |
| Age, years                     |                | -0.987 | 0.275 | -0.319 | 0.001   |
| Total cholesterol, mg/dl       |                | 0.020  | 0.023 | 0.095  | 0.388   |
| HDL cholesterol, mg/dl         |                | 0.158  | 0.064 | 0.261  | 0.014   |
| Model 2                        | 0.237          |        |       |        |         |
| Age, years                     |                | -0.717 | 0.278 | -0.233 | 0.011   |
| Education, years               |                | 0.485  | 0.183 | 0.242  | 0.009   |
| HDL cholesterol, mg/dl         |                | 0.157  | 0.059 | 0.240  | 0.009   |
| Model 3                        | 0.487          |        |       |        |         |
| Age, years                     |                | -0.242 | 0.254 | -0.080 | 0.343   |
| Education, years               |                | 0.374  | 0.156 | 0.190  | 0.019   |
| SPPB                           |                | -0.069 | 0.223 | -0.033 | 0.759   |
| BADL                           |                | -2.242 | 0.658 | -0.412 | 0.001   |
| IADL                           |                | -0.414 | 0.268 | -1.546 | 0.126   |
| HDL cholesterol, mg/dl         |                | 0.115  | 0.054 | 0.174  | 0.037   |

BMI = Body Mass Index; SPPB = Short Physical Performance Battery; BADL = Basic Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MMSE = Mini Mental State Examination

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**Table 4**

Multiple linear regression analysis of the association between demographic, clinical and functional parameters and MMSE in females (n=208)

| Dependent variable: MMSE score |                          | R <sup>2</sup> | β      | SE    | Std β  | p-value |
|--------------------------------|--------------------------|----------------|--------|-------|--------|---------|
| Model 1                        |                          | 0.222          |        |       |        |         |
|                                | Age, years               |                | -0.749 | 0.157 | -0.267 | <0.0001 |
|                                | BMI, kg/m <sup>2</sup>   |                | 0.346  | 0.103 | 0.188  | 0.001   |
|                                | Total cholesterol, mg/dl |                | 0.020  | 0.018 | 0.089  | 0.255   |
|                                | HDL cholesterol, mg/dl   |                | 0.140  | 0.041 | 0.272  | 0.001   |
| Model 2                        |                          | 0.227          |        |       |        |         |
|                                | Age, years               |                | -0.695 | 0.122 | -0.377 | <0.0001 |
|                                | BMI, kg/m <sup>2</sup>   |                | 0.085  | 0.074 | 0.076  | 0.248   |
|                                | Cohabitation status      |                | -1.849 | 0.684 | -0.180 | 0.008   |
|                                | Depression               |                | -2.457 | 1.210 | -0.134 | 0.044   |
|                                | HDL cholesterol, mg/dl   |                | 0.034  | 0.022 | 0.102  | 0.125   |
| Model 3                        |                          | 0.391          |        |       |        |         |
|                                | Age, years               |                | -0.375 | 0.123 | -0.202 | 0.003   |
|                                | BMI, kg/m <sup>2</sup>   |                | 0.095  | 0.069 | 0.084  | 0.173   |
|                                | Cohabitation status      |                | -0.400 | 0.668 | -0.039 | 0.551   |
|                                | Depression               |                | -0.165 | 1.190 | -0.009 | 0.890   |
|                                | Cardiovascular disease   |                | 1.133  | 0.711 | 0.097  | 0.113   |
|                                | Antipsychotics           |                | -0.389 | 1.566 | -0.015 | 0.804   |
|                                | SPPB                     |                | 0.228  | 0.146 | 0.123  | 0.119   |
|                                | BADL                     |                | -0.464 | 0.337 | -0.124 | 0.170   |
|                                | IADL                     |                | -0.545 | 0.166 | -0.310 | 0.001   |
|                                | HDL cholesterol, mg/dl   |                | 0.016  | 0.021 | 0.047  | 0.452   |

BMI = Body Mass Index; SPPB = Short Physical Performance Battery; BADL = Basic Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MMSE = Mini Mental State Examination

cognitive performance.

In the present study we were not able to find a significant association between HDL cholesterol and cognitive measures in females. Gender differences in brain pathophysiology and dementia development have been reported in the literature (20), and in all population studies that include cohorts of very elderly people, females represent the large part of the population. However, in the Mugello study, as in other population studies that include very old people, this higher prevalence of females is not perfectly linked to a better state of health in terms of co-morbidity, functional and cognitive measures (21). In our cohort the females are significantly older, with a low level of education and with a greater prevalence of depression as a comorbidity than males. By conducting a complete statistical model with adjustment for possible confounding factors the association between lipid variables and cognitive measures disappears, possibly related to these differences in terms of demographic, clinical and functional variables. In the same cohort of subjects, we have recently demonstrated that depression is somewhat related to dietary variables as well as

lifestyle factors, by possibly hypothesizing the role of other confounding factors in the development, onset and progression of this comorbidity that can significantly affect cognitive functions (22).

This study has the main limitation of the cross-sectional nature of its findings. Only a longitudinal analysis of the results would help to validate the results on the possible relationship between lipid variables, and in particular HDL cholesterol and cognitive function. However, this study has the strength to be one of the largest study population including only nonagenarians to whom a series of various instrumental examinations and evaluations have been performed.

In conclusion, the results of the present study suggest that focusing on HDL cholesterol than on total cholesterol alone seems much more useful for understanding the relationship between lipid variables and cognitive measures. Strategies such as changing lifestyle behaviors that can increase HDL levels, such as taking regular physical activity and eating a healthy, low-fat diet should continue to be recommended.

*Ethics approval and consent to participate:* The protocol of the Mugello study was in accordance with the principles of the Declaration of Helsinki on clinical research involving human beings and was approved by the Ethical Committee of the Don Gnocchi Foundation.

*Competing interests:* The authors declare that they have no competing interests.

*Funding:* Founded by the Italian ministry of health (current research 2012-2016).

*Authors' contributions:* Study concept and design: CM, FC and Mugello Study Group. Acquisition of subjects and/or data: FC and Mugello Study Group. Analysis and interpretation of data: SP, FS. Preparation of manuscript: SP, FS. Revision of the manuscript: CM, FC. All authors read and approved the final version of the manuscript.

*Acknowledgements:* The Mugello Study Working Group also includes: Raffaele Molino Lova, Federica Vannetti, Guido Pasquini, Laura Fabbri, Filippo Gerli, Leonardo Martini, Irene Mosca, Annamaria Gori, Nona Turcan, Debora Valecchi, Roberta Frandi, Lorenzo Razzolini, Valentina Fabbri, Guglielmo Bonaccorsi, Chiara Lorini, Roberta Boni, Chiara Castagnoli, Anita Paperini, Luca Padua.

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