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NAFLD and cognitive decline in older adults: a longitudinal cohort study

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Abstract

Nonalcoholic Fatty Liver Disease (NAFLD) is increasing in older adults, but no evidence exists on the longitudinal association between NAFLD and cognitive decline at old ages. The aim of this 7-year longitudinal study was to examine whether presence of NAFLD at baseline and/or its change (i.e. progression or regression) over the follow up predict the rate of cognitive decline over the same timeframe in older adults, independent of potential confounders. Participants included 457 community dwelling men and women aged 65 to 87 (mean ±SD: 70.9±4.1) years old, living near Bologna (Northern Italy). Global cognitive status was evaluated using Mini-mental State Examination (MMSE). Hepatic steatosis was assessed by abdominal ultrasound and categorized as absent, mild, moderate or severe. Participants were also classified into three subgroups according to their progression, stability or regression in hepatic steatosis over the follow up. Generalized estimating equation (GEE) models with 30 minus MMSE total score as the dependent variable with a Poisson distribution were used to test the longitudinal associations. Covariates included demographics, education, activities of daily living, alcohol, smoke, body mass index (BMI), waist circumference, hypertension, dyslipidemia, diabetes, insulin resistance and inflammation. As results, I found no significant association between baseline presence/severity of hepatic steatosis and either cross-sectional cognitive status or longitudinal rate of cognitive decline (P> .05). In addition, participants who underwent regression in the degree of hepatic steatosis over the follow-up presented accelerate cognitive decline over the same timeframe compared to the rest of the population, independent of covariates and even after adjusting for longitudinal change in BMI and waist circumference (P= .03). A nested sensitivity analysis confirmed this trend even when including only participants starting from moderate-severe hepatic steatosis at baseline. In conclusion, the present study suggests that in older adults NAFLD regression rather than progression is associated with accelerated cognitive decline.

Introduction

NALFD definition, pathogenesis and epidemiology

Nonalcoholic Fatty Liver Disease (NAFLD) is a pathological condition characterized by excessive hepatic fat accumulation associated with insulin resistance and defined by the presence of hepatic steatosis on either imaging or histology in individuals without excessive alcohol consumption (<20 g/day for women and <30 g/day for men) or other competing causes of liver disease[1,2]. It is a multifactorial and multisystem disease resulting from complex genetics, environmental and metabolic interactions[2-4]. It currently affects about 25% of the world population and it is one of the most common cause of chronic liver disease[5, 6]. It has been estimated that the burden of NAFLD will even increase worldwide in the next decades with a tremendous clinical and economic impact[7].

NAFLD and aging

Aging is characterized by major changes in body composition that negatively affect functional status and outcomes in older adults. Particularly, at old ages (≥ 70 years), both fat-free mass and fat mass tend to decrease, with consequent decreasing body weight. Moreover, visceral fat tends to increase with aging, while subcutaneous fat declines, resulting in increased insulin resistance[8]. Therefore, aging is considered a risk factor for NAFLD. Consistently, data from a recent meta-analysis showed that the NAFLD prevalence increases with aging, although studies about NAFLD in individuals aged 70 years or older are very limited[5].

Due to the growing burden of NAFLD and the population aging, the number of older adults with NAFLD is rising and is expected to rise even more in the next decades.

There is a general agreement on the fact that presence of NAFLD in young and middle aged adults has a negative prognostic meaning because it increases the risk for type-2 diabetes, metabolic syndrome and cardiovascular diseases[3]. However, how the presence of NAFLD at old ages affects prognosis and relates to the main geriatric outcomes is still unclear and not exhaustively investigated.

NAFLD and cognition

Previous evidence demonstrated that middle-aged adults with NAFLD present a greater risk of cognitive decline and dementia compared to those without NAFLD. Noteworthy, a large cross-sectional epidemiological study, enrolling in 4,472 adults aged between 20 and 59 year old participating in the NHANES III, found that NAFLD was independently associated with lower

cognitive performance independent of CVD and its risk factors[9]. Carotid atherosclerosis, insulin resistance, inflammation and hormonal alterations have been proposed as causal mechanisms for this association[8, 9]. Interestingly, NAFLD was associated with lower brain volume in 766 middle-aged adults in the Framingham Study[10]. However, whether a positive association between NAFLD and cognitive decline holds also at advanced ages and even longitudinally is still unclear. A recent study in individuals aged 60 years or older showed that participants with both NAFLD and T2DM had lower cognitive performance, but not those with NAFLD only[11]. Moreover, whether the presence NAFLD at advanced ages (≥ 65 years) should be considered a risk factor for subsequent faster cognitive decline remains unknown. Likewise, how NAFLD progression or regression overtime in the elderly may affect their rate of cognitive decline has never been formally investigated.

Therefore, using data from 457 community dwelling older adults, living in Pianoro, Northern Italy, and followed for 7 years (2003-2010), the present study explored the longitudinal association between NAFLD and cognitive decline. Participants with available information both at baseline and at 7-year follow-up visit on presence/severity of hepatic steatosis assessed using abdominal ultrasound and global cognitive function evaluated using Mini-Mental State Examination (MMSE) and without excessive alcohol consumption or other competing causes of hepatic steatosis were included. Particularly, the aim of the study was to investigate whether the presence/severity of hepatic steatosis at baseline and/or its progression/regression over the time of follow-up may be associated with the rate of cognitive decline over the same timeframe, independent of potential confounders.

Methods

Study design and setting

The Pianoro study is an epidemiological study enrolling men and women aged 65 years or more, living in Pianoro, near Bologna, Northen Italy. Detailed characteristics of the study have been previously provided[12, 13]. Briefly, baseline information about lifestyle, risk factors for atherosclerosis, previous cardiovascular diseases and drugs were collected by self-reported questionnaires. Moreover, participants underwent clinical, laboratory and instrumental investigations, including abdominal ultrasound assessment, at the Internal Medicine Unit of the

S. Orsola-Malpighi Hospital in Bologna, led by Professor Marco Zoli. Overall, 1142 subjects underwent baseline visit and, of these, 476 underwent a 7-year follow up visit. Those who had uncomplete longitudinal data on NAFLD and cognitive decline and/or reported a significant alcohol consumption (n=19) were excluded. Thus, 457 participants were included in the present longitudinal analysis.

Of note, the joint ethics committee of Bologna University and S. Orsola Malpighi Hospital approved the Pianoro Study.

Participants

The sample for the present analysis consists of 457 participants aged 65 to 87 (mean ±SD: 70.9±4.1) years old, of whom 225 (49.2%) were men, with no significant alcohol consumption (<two units/day) and available data on hepatic steatosis and cognitive performance both at baseline and at 7-year follow up visit.

Covariates

Years of *education* were self-reported and collected as none, five years, eight years, thirteen years or more than thirteen year based on the Italian Education System. Specifically, for the present analysis, poor education was defined as five years or less. *Alcohol intake* was defined as the daily use of at least one alcoholic unit (a glass of wine or a pint of beer or a small glass of spirit). *Smoking status* (nonsmokers, former smokers or current smokers) was self-reported. Weight in kilograms (kg) and height in meters (m) were assessed and used to calculate *BMI* (kg/m^2). *Waist circumference* was measured in centimeters (cm) with the patient standing at the umbilicus level. *Activities of Daily Living (ADL) scale*[14] and *Instrumental Activities of Daily Living (IADL) scale*[15] were used to assess functional capacity in basic and more complex activities of daily living of the study participants. *Hypertension* was defined as a systolic blood pressure (SBP) ≥140 mmHg and/or a diastolic blood pressure (DBP) ≥90 mmHg, and/or patients being treated with antihypertensive medication. *Hyperlipidemia* was defined as total serum cholesterol ≥200 mg/dL and/or LDL cholesterol ≥160 mg/dL and/or HDL cholesterol < 40 mg/dl and/or any concurrent pharmacologic lipid-lowering treatment[16]. Diagnosis of *diabetes* was based on a history of diabetes according to the American Diabetes Association Criteria, and/or on assumptions of anti-diabetes drugs[17]. Moreover, baseline insulin was measured using an electrochemiluminescence immunoassay (Insulin Elecsys; Roche Diagnostics). Baseline *insulin resistance* was then estimated, according to the homeostasis

model assessment (HOMA), using the formula: (fasting insulin [mU/l] x fasting glucose [mmol/l])/22.5[18]. Finally, baseline serum levels of interleukin 6 (IL-6) were also measured using multiplex beads immunoassay (Bio-Rad Laboratories, Hercules, CA, USA) [19].

Hepatic steatosis

The evaluation of steatosis, defined at ultrasound scan, as the presence of "bright liver", was made both at baseline and 7-year follow up visits by two skilled operators using an *Esoate-Ansaldo Technos* echograph with a 3.5–5 MHz convex ultrasound probe. In particular, steatosis was classified into three degrees:

-*Mild* when hyperechogenicity of hepatic parenchyma compared to renal parenchyma was present, in absence of attenuation of the ultrasound beam,

-*Moderate* when attenuation of the ultrasound beam was present,

-*Severe* when a marked attenuation of the ultrasound beam, such as not to make visible the portal bifurcation, was present.

For the present analysis, we categorized presence/severity of hepatic steatosis in 0.absence of hepatic steatosis; 1.mild hepatic steatosis; 2.moderate hepatic steatosis; 3.severe hepatic steatosis. For each participant, difference in presence/severity of hepatic steatosis between the 7-year follow up visit and the baseline visit was also calculated. In addition, participants were classified into three categories according to their progression, stability or regression in hepatic steatosis overtime.

Cognitive status

Global cognitive status was assessed using the Mini-mental State Examination (MMSE), a standardized 30-point questionnaire extensively used in clinical and research setting to screen for cognitive impairment in older adults[20].

Statistical analysis

Baseline characteristics of the population are presented as mean (± standard deviation, SD), median (range interquartile) or number (percentage) in the overall population and according to progression, stability or regression in hepatic steatosis overtime. ANOVA or Kruskal-Wallis or Chi-square test were used to compare subgroups.

Generalized estimating equation (GEE) models with 30 minus MMSE total score as the dependent variables with a Poisson distribution were used to describe the average longitudinal

rate of change in cognitive function over the time of follow – up[21]. An exchangeable covariance structure was assumed. GEE modes were also used to test whether baseline presence/severity of hepatic steatosis and/or its progression/regression overtime predicted longitudinal rate of change in cognitive function while adjusting for covariates. For all the predictive variables "predictor", "time" and "predictor*time" interaction term were included in the models. Of note, because a GEE Poisson model was used with 30-MMSE as the dependent variable, the parameter estimates in the result tables have been transformed accordingly to be interpreted meaningfully[21].

Finally, a nested sensitivity analysis including only participants with moderate-severe hepatic steatosis at baseline was performed.

All analyses were performed using the SAS statistical package, version 9.3 (SAS institute Inc., Cary, NC) and R 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Hepatic steatosis

Hepatic steatosis was present at baseline in 211 participants (46.2%). In particular, 127 participants (27.8%) had mild steatosis, 74 participants (16.2%) had moderate steatosis and 10 participants (2.2%) had severe steatosis. After 7 years, hepatic steatosis was present in 180 participants (39.4%). In particular, 122 participants (26.7%) had mild steatosis, 55 participants (12%) had moderate steatosis and three participants (0.7%) had severe steatosis. Therefore, on average, prevalence and severity of steatosis decreased over the time of the study. Specifically, 106 participants showed a regression of hepatic steatosis, while only 49 a progression; the others were stable. Baseline characteristics for the overall population and according steatosis regression, stability or progression are presented in Table 1. Briefly, participants who underwent regression in hepatic steatosis overtime started from a higher degree of hepatic steatosis at baseline and they had greater baseline BMI, waist circumference and insulin resistance compared to the rest of the population.

Cognition

Overall, in the present study population median values [interquartile range] of MMSE score went from 28 [26–29] at baseline evaluation to 27 [25–29] at the follow up evaluation.

At baseline, older age and poor education were significantly associated with lower cross-sectional cognitive performance.

Moreover, independent of baseline age, sex and education, MMSE significantly declined with aging over the follow up (the average longitudinal rate of decline in MMSE, estimated using GEE model, was - 0.024 (±0.006) point per year, $P < .001$). A greater baseline age was significantly associated with faster longitudinal cognitive decline (P=.005), while no significant sex difference were found (supplemental material S1).

Baseline presence and severity of hepatic steatosis and cognition

I also used GEE model to test whether baseline presence and severity of hepatic steatosis was associated with cross-sectional cognitive status and/or longitudinal rate of change in cognitive status, independent of baseline age, sex and level of education. As shown in Table 2, I found no significant cross-sectional or longitudinal associations between baseline presence/severity of hepatic steatosis and cognitive status.

Overtime hepatic steatosis regression, stability or progression and cognition

Then, I explored the association between hepatic steatosis regression, stability or progression over the time of the follow up and rate of change in cognitive status over the same timeframe. Firstly, I observed that the difference between MMSE at baseline and MMSE at 7-year follow up visit was greater in individuals who presented NAFLD regression over the time of the follow up compared to the rest of the population, even after adjusting for baseline age, sex, education, baseline presence/severity of hepatic steatosis and baseline MMSE (Figure1). Then, performing GEE models, I confirmed that participants who underwent NAFLD regression over the time of the study had a more accelerated cognitive decline over the same time of the study, independent of baseline age, sex and education (P=.037, Table 3 and Supplemental Material S2). As show in Figure 2, participants who underwent steatosis regression overtime (red lines) had steeper longitudinal trajectories of decline overtime in MMSE over the 7-year follow up compared to the rest of the population (gray lines). This result was confirmed even after adjusting for a comprehensive set of potential confounders (fully adjusted model, Table 3). In particular, the significant association held also when adjusted for baseline BMI and longitudinal change in

BMI as well as baseline waist circumference and longitudinal change in waist circumference (Table 3 and Supplemental Materials S3-S4). The results were analogous when adjusting for time-varying BMI and time-varying waist circumference (not shown). On the other hand, in the present sample population longitudinal change in BMI and longitudinal change in waist circumference were not significantly associated with longitudinal rate of decline in cognitive status (Supplemental Materials S5-S7).

Nested sensitivity analysis

Although all previous analyses were adjusted for baseline severity of hepatic steatosis, because participants who underwent NAFLD regression overtime started from a more severe baseline degree of hepatic steatosis, I performed a nested sensitivity analysis to definitively exclude that it may represent a bias. Therefore, I ran a further analysis including only participants with moderate-severe hepatic steatosis at baseline comparing those who underwent NADFL regression (n=49) to those who did not (n=35). Although the analysis did not reach statistical significance due to the small size of the sample, the results for this nested analyses followed the same trend of the overall analysis. Specifically, as shown in Figure 3, those who underwent NAFLD regression tend to have a steeper decline in MMSE overtime compare to those who showed NAFLD stability or progression, confirming the results of overall analysis.

Discussion

Using longitudinal data from a cohort of 457 older adults, the present study investigated whether the presence/severity of hepatic steatosis at baseline and/or its progression/regression over the time of the follow-up may be associated with the rate of cognitive decline over the same timeframe, independent of potential confounders. No significant associations were found between presence/severity of hepatic steatosis at baseline and either cross-sectional cognitive status or rate of decline overtime in cognitive performance. Moreover, participants who underwent regression in the degree of hepatic steatosis over the follow-up time presented accelerate cognitive decline over the same timeframe compared to the rest of the population, independent of hepatic steatosis severity at baseline and other potential confounders. Particularly, such associations remained significant even when adjusting for baseline BMI and

longitudinal change in BMI as well as baseline waist circumference and longitudinal change in waist circumference.

NAFLD in middle-aged adults is an undeniable risk factor for type 2 diabetes, metabolic syndrome and cardiovascular disease [4, 22]. Moreover, the presence of NAFLD in middle-aged adults is associated with higher risk of future accelerated cognitive decline, mainly due to greater carotid atherosclerosis, insulin resistance and pro-inflammatory status [23-25]. However, the relationship between NAFLD at advanced ages and cognitive performance has never been exhaustively investigated so far. For example, a previous study found that NAFLD associated with type 2 diabetes but not NAFLD alone is associated with cross-sectional lower cognitive performance in individuals aged 60 years or older [11]. In addition, to my best knowledge, this is the first study investigating the longitudinal association between NAFLD and cognitive decline in older adults.

Noteworthy, I found that NAFLD regression rather than progression was associated with accelerated cognitive decline.

The biological mechanisms underlying such association remain unclear.

However, weight loss is recognized as the most effective way to promote liver fat removal [26]. Moreover, while midlife obesity is mainly considered a risk factor for dementia [27-29], at old ages loss of weight has been linked to cognitive decline and development of dementia [30-32]. Nevertheless, whether the loss of weigh in late life is the result of or contributes to dementia is controversial. If fact, loss of weight may occur at a preclinical stage in the disease history and begin several years before the diagnosis of the disease. In particular, loss of weight may precede the onset of dementia, suggesting that pathological processes underlying loss of weight may contribute to the subsequent cognitive decline [33]. On the other hand, the loss of weight may be the result of the occurrence of a wasting chronic condition rather than the cause (reverse causation) [34]. Specifically, loss of weight may also be an early manifestation of dementia [35]. Plausible explanations include malnutrition and increased catabolic status.

Therefore, a pathologic loss of weight, that is often associated with cognitive decline, may be responsible for the disappearance of the liver fat deposits and it may have biased the results of my analysis. However, I addressed this issue running an additional analysis including change in weight overtime as a covariate and the original findings were confirmed (S8 in Supplemental Materials).

Consistently with the results of the present study, previous researches showed that in the geriatric population metabolic syndrome and traditional risk factors for cardiovascular disease

relate to adverse outcomes in the opposite direction compared to young and middle-aged persons [36, 37]. Some examples include the "reverse metabolic syndrome" and the "obesity paradox". In fact, contrary to what happens at younger ages, having metabolic syndrome and/or being overweight at advanced ages have been found to be protective from mortality [38-41].

Loss of weight is also one of the criteria to define the frailty syndrome [42].

In addition, in a previous research I performed at the Intramural Research Program of the National Institute on Aging (NIA/NIH) under the leadership of Dr. Luigi Ferrucci, I found that loss of weight rather than weight gain was associated with longitudinal expansion of burden of multimorbidity in obese older adults enrolled in the InChianti Study [43].

Overall, these findings suggest that loss of fatness in the elderly is a maker of impending deterioration of physical and cognitive health.

Another important consideration concerns the regional distribution of adiposity. In fact, it has been proposed that visceral adiposity may be a better predictor of cognitive decline compared to total body fat mass. Therefore, it was suggested that the combination of central obesity (i.e. waist circumference) and overall obesity (i.e. BMI) might be more predictive of cognitive performance than either measure alone [44]. However, in the present study no significant associations were found for either change in BMI or change in waist circumference overtime and cognitive decline. In addition, the significant association between change in degree of hepatic steatosis and cognitive decline held also while adjusting for both these covariates, suggesting that the assessment of change overtime in the degree of hepatic steatosis is even more meaningful and informative than the assessment of change in anthropometric measures alone.

Points of strengths of the present study include presence of NAFLD defined by abdomen ultrasound (not always available in epidemiological studies on aging) and longitudinal design. However, some limitations need to be addressed. First, the study population is from a small Italian town, so further studies in larger and different populations are required to validate and generalize these findings. Second, more than 50% of the original population enrolled the Pianoro Study was excluded from the current analysis because no longitudinal data were available (S9 in Supplemental Materials). Since the excluded participants were significantly older and sicker (as they were taking a greater number of medications) than the included ones (S10 in Supplemental Materials), this may represent a "healthy selection bias". Moreover, competing mortality may have affected my results. However, based on the evidence about the paradoxical relationship about adiposity and mortality in the geriatric population that I

presented in the body of the discussion, it is reasonable to think that those who died would have had NAFLD regression rather than stability or progression so this would actually confirm and reinforce my results.
Furthermore, I acknowledge that, because change in degree of hepatic steatosis and change in cognitive status occurred within the same timeframe, cause–effect relationships cannot be inferred. Besides, the present study included only one cognitive test, specifically MMSE. Other studies are required to test the association across a wider range of cognitive tests. Finally, it would be interesting to evaluate the association between longitudinal NAFLD regression or progression and the parallel change in physical function. However, in the Pianoro Study no longitudinal measures of physical function are available.

In conclusion, this study found that NAFLD regression compared to NAFLD stability or progression is associated with accelerated cognitive decline in older adults, independent of potential confounders. Although further investigations are required to validate these results and to fully understand the underlying biological mechanisms, this study supports the hypothesis of a paradoxical relationship between traditional cardiovascular risk factors and adverse outcomes in late life.

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Tables and Figures

Table1. Baseline of characteristics of the study population in the overall sample (n=457) and according to overtime hepatic steatosis regression (n=106), stability (n=302) and progression (n=49).

	All (n=457)	**Steatosis regression (n=106)**	**Steatosis stability (n=302)**	**Steatosis progression (n=49)**	**P value ***
Age (years)	70.9 (±4.1)	71.6 (±4.4)	70.7 (±3.9)	70.5 (±4.1)	.108
Sex (men)	225 (49.2%)	60 (56.6%)	144 (47.7%)	21 (42.8%)	.183
Education ≤5 years	281 (61.5%)	72 (67.9%)	177 (58.6%)	32 (65.3%)	.201
Alcohol intake (units/day)	1 [0-1]	1 [0-1]	1 [0-1]	1 [0-1]	.225
Ex-Smokers	149 (32.6%)	42 (39.6%)	92 (30.5%)	15 (30.6%)	.213
Current smokers	45 (9.8%)	8 (7.5%)	32 (10.6%)	5 (10.2%)	.660
ADL deficit	129 (28.3%)	36 (33.9%)	80 (26.5%)	13 (27.1%)	.333
IADL deficit	254 (55.7)	65 (61.3%)	167 (55.3%)	22 (45.8%)	.195
MMSE	28 [26-29]	27 [26-29]	28 [26-29]	27 [25-29]	.889
BMI (kg/m^2)	26.6 (±3.8)	28.4 (±3.8)	25.9 (±3.7)	27.1 (±3.3)	<.001
Waist circumference (cm)	96.2 (±11.1)	111.4 (±10.0)	94.3 (±11.2)	96.9 (±8.8)	<.001
Hypertension	382 (84.3%)	93 (87.7%)	249 (83.3%)	40 (83.3%)	.544
Hyperlipidemia	377 (82.5%)	86 (81.1%)	252 (83.4%)	39 (79.6%)	.737
Diabetes	59 (12.9%)	17 (16.0%)	36 (11.9%)	6 (12.2 %)	.547
HOMA index	1.94 [1.35-3.04]	2.47 [1.59-3.99]	1.78 [1.26-2.81]	2.23 [1.63-3.11]	<.001
Serum IL 6 (pg/ml)	3.44 [2.06-5.92]	3.93 [2.38-6.00]	3.43 [1.82-6.21]	2.90 [1.96-5.20]	.181
Hepatic steatosis severity	0 [0-1]	1[1-2]	0 [0-1]	0 [0-1]	<.001

Table 2. Generalized estimating equation (GEE) model testing whether baseline presence/severity of hepatic steatosis predicts longitudinal rate of change in cognitive status while adjusting for baseline age, sex and level of education.

	Cognitive status (MMSE)		
	Estimate	**Standard error**	**P value**
Baseline age (years)	-0.031	0.009	.001
Sex (men)	0.007	0.082	.929
Education ≤ 5 years	-0.687	0.089	<.001
Baseline presence/severity of hepatic steatosis	0.019	0.048	.683
Time	-0.024	0.006	<.001
Baseline age (years) *time	-0.004	0.001	.005
Sex (men) *time	-0.001	0.012	.904
Education ≤ 5 years *time	0.017	0.013	.201
Baseline presence/severity of hepatic steatosis *time	-0.005	0.007	.454

Table 3. Generalized estimating equation (GEE) models testing whether regression in hepatic steatosis overtime predicts longitudinal rate of change in cognitive status while adjusting for covariates.

	Cognitive status (MMSE)			
	Time		**Regression in hepatic steatosis*time**	
	Estimate (SE)	**P value**	**Estimate (SE)**	**P value**
Model I *	-0.024 (0.006)	<.001	-0.036 (0.017)	.037
Model II **	-0.024 (0.006)	<.001	-0.036 (0.017)	.036
Model III ***	-0.023 (0.006)	<.001	-0.034 (0.017)	.043
Model IV ****	-0.020 (0.006)	.002	-0.040 (0.019)	.035

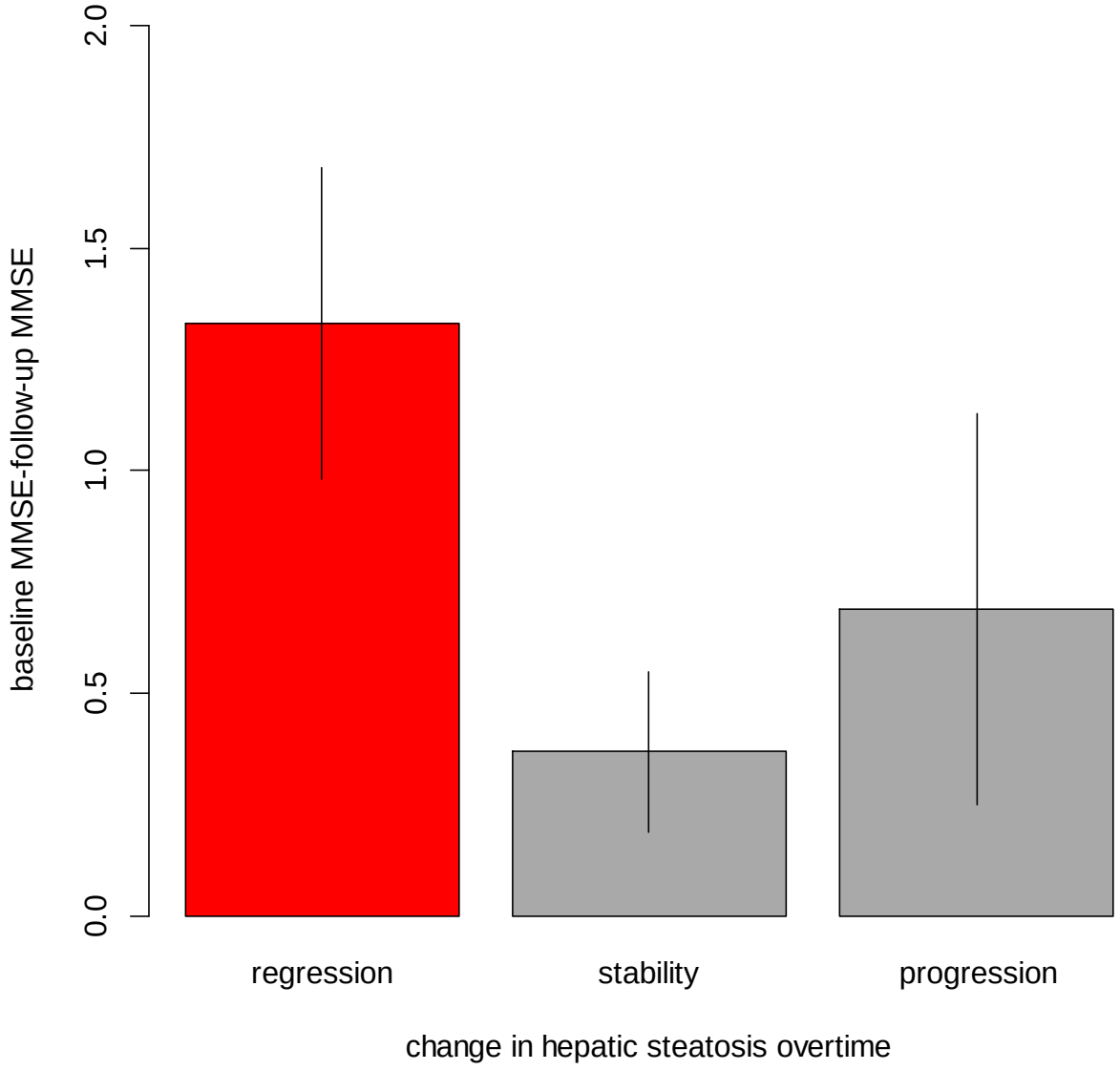
* adjusted for baseline age, sex, education and baseline severity of hepatic steatosis

** adjusted for covariates in Model I + baseline BMI and longitudinal change in BMI

*** adjusted for covariates in Model II + baseline waist circumference and longitudinal change in waist circumference

**** adjusted for covariates in Model III + smoking status, alcohol intake, present or incident diabetes, hypertension and hyperlipidemia, baseline and longitudinal change in ADL and IADL, baseline levels of IL6 and insulin resistance (HOMA index)

Figure1. Average longitudinal change in MMSE (MMSE at baseline visit – MMSE at 7-year follow up visit) according to steatosis regression (red box), stability (black box) or progression (blue box) and adjusted for baseline age, sex, level of education, baseline presence/severity hepatic steatosis and baseline MMSE score.



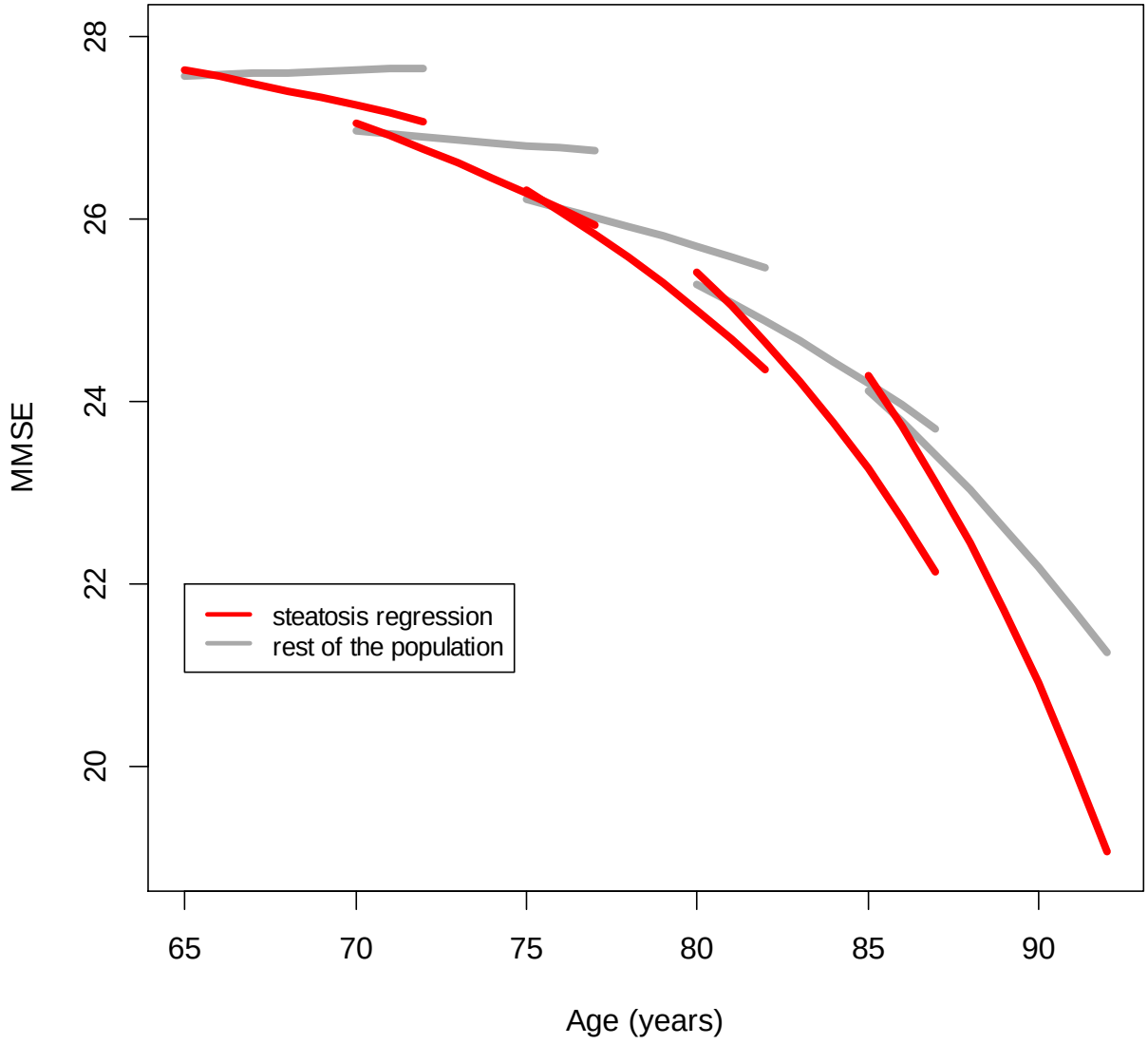
Note:

Regression versus rest of the population: P value <.05

Regression versus stability: P value <.05

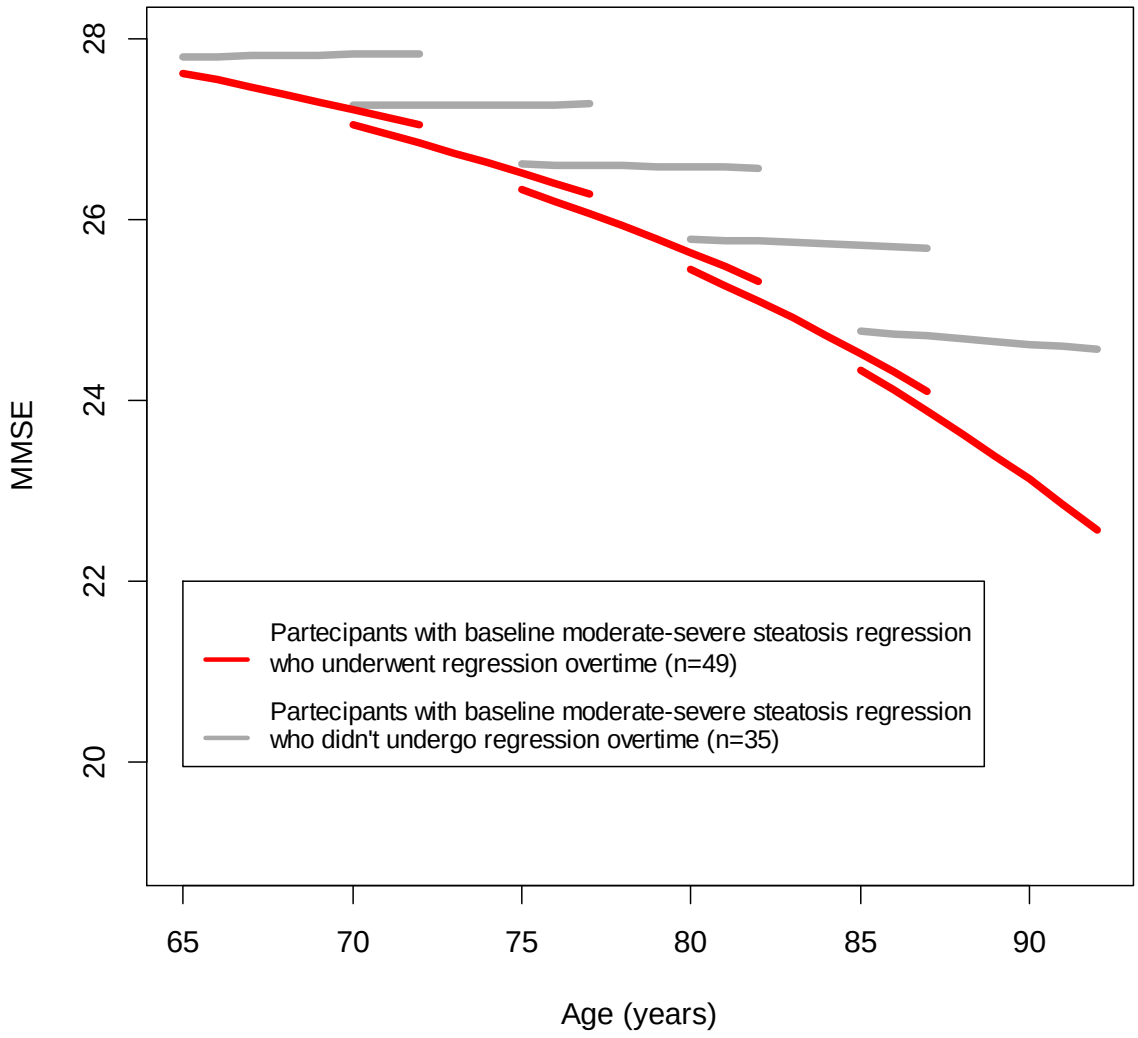
Regression versus progression: P value >.05

Figure2. Longitudinal trajectories of decline in MMSE over the 7-year follow up in participants who underwent steatosis regression overtime (red lines) versus the rest of the population (gray lines) according to different baseline age group (65-69, 70-74, 75-79, 84, 85+).



Note: P value <.05

Figure 3. Nested sensitivity analysis including only participants with moderate-severe hepatic steatosis at baseline and comparing those who underwent steatosis regression overtime (red lines) versus those who did not (gray lines).



Supplemental Materials

S1. Generalized estimating equation (GEE) model estimating the average longitudinal rate of decline in MMSE independent of age, sex and education.

	Cognitive status (MMSE)		
	Estimate	**Standard error**	**P value**
Baseline age (years)	-0.031	0.009	.001
Sex (men)	0.003	0.081	.968
Education ≤ 5 years	-0.684	0.089	<.001
Time	-0.024	0.006	<.001
Baseline age (years) *time	-0.004	0.001	.005
Sex (men) *time	-0.001	0.012	.942
Education ≤ 5 years *time	0.017	0.013	.212

S2. Generalized estimating equation (GEE) model testing whether regression in hepatic steatosis overtime predicts longitudinal rate of change in cognitive status while adjusting for baseline age, sex, education and baseline presence/severity of hepatic steatosis.

	Cognitive status (MMSE)		
	Estimate	**Standard error**	**P value**
Baseline age (years)	-0.032	0.009	.001
Sex (men)	0.008	0.082	.919
Education ≤ 5 years	-0.685	0.089	<.001
Baseline presence/severity of hepatic steatosis	0.009	0.065	.894
Regression in hepatic steatosis	0.039	0.125	.756
Time	-0.024	0.006	<.001
Baseline age (years) *time	-0.003	0.001	.018
Sex (men) *time	-0.003	0.012	.794
Education ≤ 5 years *time	0.017	0.013	.189
Baseline presence/severity of hepatic steatosis *time	0.007	0.009	.416
Regression in hepatic steatosis*time	-0.036	0.017	.037

S3. Generalized estimating equation (GEE) model testing whether regression in hepatic steatosis overtime predicts longitudinal rate of change in cognitive status while adjusting for baseline age, sex, education, baseline presence/severity of hepatic steatosis, baseline BMI and change overtime in BMI.

	Cognitive status (MMSE)		
	Estimate	**Standard error**	**P value**
Baseline age (years)	-0.033	0.010	.001
Sex (men)	0.012	0.082	.882
Education ≤5 years	-0.682	0.089	<.001
Baseline BMI	0.002	0.012	.839
Longitudinal change in BMI	0.011	0.024	.648
Baseline presence/severity of hepatic steatosis	0.006	0.072	.938
Regression in hepatic steatosis	0.027	0.127	.831
Time	-0.024	0.006	<.001
Baseline age (years) *time	-0.003	0.001	.021
Sex (men) *time	-0.004	0.012	.719
Education ≤ 5 years *time	0.018	0.013	.177
Baseline BMI *time	-0.002	0.002	.188
Longitudinal change in BMI *time	0.001	0.003	.807
Baseline presence/severity of hepatic steatosis *time	0.012	0.009	.221
Regression in hepatic steatosis*time	-0.036	0.017	.036

S4. Generalized estimating equation (GEE) model testing whether regression in hepatic steatosis overtime predicts longitudinal rate of change in cognitive status while adjusting for baseline age, sex, education, baseline presence/severity of hepatic steatosis, baseline BMI, change overtime in BMI, baseline waist circumference and change overtime in waist circumference.

	Cognitive status (MMSE)		
	Estimate	**Standard error**	**P value**
Baseline age (years)	-0.032	0.011	.003
Sex (men)	0.017	0.084	.843
Education ≤5 years	-0.674	0.090	<.001
Baseline BMI	0.017	0.021	.425
Longitudinal change in BMI	0.021	0.027	.438
Baseline waist circumference	-0.006	0.007	.369
Longitudinal change in waist circumference	0.005	0.008	.493
Baseline presence/severity of hepatic steatosis	0.014	0.072	.845
Regression in hepatic steatosis	0.019	0.127	.881
Time	-0.023	0.006	<.001
Baseline age (years) *time	-0.004	0.002	.013
Sex (men) *time	-0.001	0.012	.936
Education ≤ 5 years *time	0.018	0.013	.181
Baseline BMI *time	-0.005	0.003	.075
Longitudinal change in BMI *time	-0.001	0.004	.859
Baseline waist circumference	0.001	0.001	.207

Longitudinal change in waist circumference	0.001	0.001	.602
Baseline presence/severity of hepatic steatosis *time	0.010	0.009	.304
Regression in hepatic steatosis*time	-0.034	0.017	.043

S5. Generalized estimating equation (GEE) model testing whether change overtime in BMI predicts longitudinal rate of change in cognitive status while adjusting for baseline age, sex, education and baseline BMI.

	Cognitive status (MMSE)		
	Estimate	**Standard error**	**P value**
Baseline age (years)	-0.032	0.010	.001
Sex (men)	0.011	0.083	.891
Education ≤5 years	-0.682	0.089	<.001
Baseline BMI	0.003	0.010	.735
Longitudinal change in BMI	0.013	0.024	.603
Time	-0.024	0.006	<.001
Baseline age (years) *time	-0.004	0.001	.009
Sex (men) *time	-0.003	0.011	.823
Education ≤ 5 years *time	0.017	0.013	.209
Baseline BMI *time	-0.002	0.001	.185
Longitudinal change in BMI *time	0.002	0.003	.441

S6. Generalized estimating equation (GEE) model testing whether change overtime in waist circumference predicts longitudinal rate of change in cognitive status while adjusting for baseline age, sex, education and baseline waist circumference.

	Cognitive status (MMSE)		
	Estimate	**Standard error**	**P value**
Baseline age (years)	-0.031	0.010	.002
Sex (men)	0.004	0.085	.956
Education ≤5 years	-0.683	0.089	<.001
Baseline waist circumference	-0.001	0.003	.838
Longitudinal change in waist circumference	0.004	0.007	.617
Time	-0.024	0.006	<.001
Baseline age (years) *time	-0.004	0.001	.006
Sex (men) *time	-0.002	0.012	.833
Education ≤ 5 years *time	0.017	0.013	.204
Baseline waist circumference	-0.0002	0.0005	.677
Longitudinal change in waist circumference	0.0005	0.0011	.648

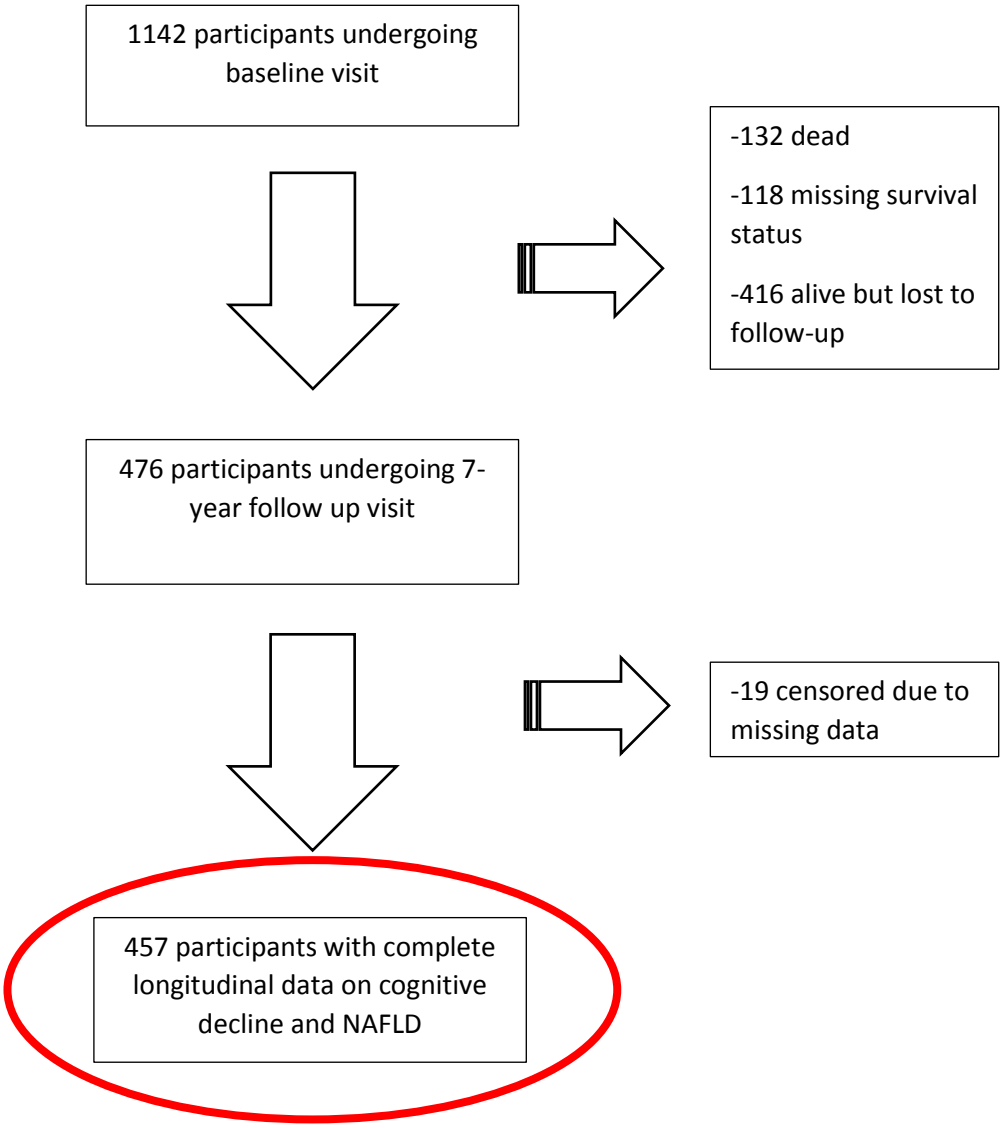
S7. Generalized estimating equation (GEE) model testing whether change overtime in BMI and/or change overtime in waist circumference predict longitudinal rate of change in cognitive status while adjusting for baseline age, sex, education, baseline BMI and baseline waist circumference.

	Cognitive status (MMSE)		
	Estimate	**Standard error**	**P value**
Baseline age (years)	-0.032	0.011	.003
Sex (men)	-0.018	0.085	.831
Education ≤5 years	-0.674	0.090	<.001
Baseline BMI	0.019	0.021	.368
Longitudinal change in BMI	-0.023	0.027	.392
Baseline waist circumference	-0.006	0.007	.362
Longitudinal change in waist circumference	0.006	0.008	.465
Time	-0.024	0.006	<.001
Baseline age (years) *time	-0.004	0.002	.006
Sex (men) *time	0.001	0.012	.929
Education ≤ 5 years *time	0.015	0.013	.216
Baseline BMI *time	-0.006	0.003	.057
Longitudinal change in BMI *time	0.001	0.004	.816
Baseline waist circumference	0.001	0.001	.170
Longitudinal change in waist circumference	0.001	0.001	.594

S8. Generalized estimating equation (GEE) model testing whether regression in hepatic steatosis overtime predicts longitudinal rate of change in cognitive status while adjusting for baseline age, sex, education, baseline presence/severity of hepatic steatosis, loss of weight overtime and time-varying height.

	Cognitive status (MMSE)		
	Estimate	**Standard error**	**P value**
Baseline age (years)	-0.033	0.010	.001
Sex (men)	0.007	0.112	.528
Education ≤5 years	-0.670	0.090	<.001
Time-varying Height (cm)	0.559	0.777	.471
Loss of weight (kg)	-0.005	0.009	.579
Baseline presence/severity of hepatic steatosis	0.011	0.066	.871
Regression in hepatic steatosis	0.028	0.128	.824
Time	-0.025	0.006	<.001
Baseline age (years) *time	-0.003	0.001	.026
Sex (men) *time	0.011	0.016	.466
Education ≤ 5 years *time	0.017	0.013	.204
Time-varying Height (cm) *time	0.108	0.098	.267
Loss of weight (kg) *time	0.001	0.001	.456
Baseline presence/severity of hepatic steatosis *time	0.006	0.009	.516
Regression in hepatic steatosis *time	-0.036	0.017	.031

S9. Design of the study



S10. Comparison of baseline characteristics between included (n=457) and excluded (n=685) participants of the Pianoro study

	Study Sample (n=457)	**Rest of baseline population (n=685)**	**P value**
Age (years)	70.9 (±4.1)	73.5 (±6.1)	<.001
Sex (men)	225 (49.2%)	325 (47.5%)	.553
Education ≤5 years	281 (61.5%)	386 (56.3%)	.084
Ex-Smokers	149 (32.6%)	198 (28.9%)	.183
Current smokers	45 (9.8%)	47 (6.8%)	.069
ADL deficit	129 (28.3%)	208 (39.1%)	<.001
IADL deficit	254 (55.7%)	353 (66.3%)	<.001
MMSE	28 [26-29]	27 [23-28]	<.001
BMI (kg/m^2)	26.6 (±3.8)	26.2 (±3.9)	.102
Hypertension	382 (84.3%)	461 (86.5%)	.336
Hyperlipidemia	377 (82.5%)	414 (77.7%)	.059
Diabetes	59 (12.9%)	106 (15.5%)	.227
Previous CV events	23 (5.03%)	52 (7.59%)	.087
Previous falls	69 (15.1%)	112 (16.3%)	.570
Number of medication	2 [1-4]	3 [2-5]	<.001
≥ 4 medications	116 (25.4%)	278 (40.6%)	<.001