SUPPLEMENTARY MATERIAL

Lipid-lowering Drugs and Slower Motor Decline in Elderly Adults

SUPPLEMENTARY METHODS

Covariates

Education was defined as: less than primary school, primary school, secondary without a baccalaureate degree, baccalaureate or university degree. Household income per month at baseline was defined as : < 5000 FF (French Francs) ; 5000 – 10000 FF ; 10000 – 15000 FF; > 15000 FF. Self-report of doctor-diagnosed coronary (CAD) or peripheral artery disease (PAD), stroke, treated diabetes mellitus, Parkinson's disease, and hip fracture. Systolic (SBP) and diastolic blood pressure (DBP) were measured, and hypertension defined as SBP(DBP) ≥140(90) mmHg or use of antihypertensive medication. Smoking history, pack-years of smoking, and alcohol consumption (grams alcohol/week) were assessed. Low physical activity was defined as walking <1 hour/day and exercising <1 time/week (at baseline and wave 5). Weight and height were measured; body mass index (BMI), was computed as weight (kilos) divided by height (meters) squared. Cognition was evaluated using the mini-mental state examination (MMSE). Participants were screened for dementia using a standardized protocol (1). Depressive symptoms were evaluated with the Center for Epidemiological Studies-Depression scale (CES-D) (2). Self-reported measures of physical functioning included: instrumental activities of daily living (IADLs; French version of the Lawton scale(3)); mobility (Rosow-Breslau scale(4)); Katz activities of daily living (5). A 4-level hierarchical disability index was defined based on these scales. Fasting blood samples were obtained at baseline to measure homocysteine, triglycerides, and total, HDL-, and LDL-cholesterol at a single laboratory.

Statistical Analysis

Propensity Scores

In sensitivity analyses, we used propensity scores to adjust for confounders (6). We first computed the probability of using LLDs at baseline with a logistic regression model including the following predictors: age, sex, BMI, height, education, depressive symptoms, MMSE score, physical activity, alcohol consumption, smoking, hypertension, diabetes mellitus, triglycerides, HDL-and LDL-cholesterol. Each participant using LLDs at baseline was matched to one non-treated participant on the propensity score in a range of ±0.05 using the SAS %MATCH macro (7). Analyses were then repeated using linear mixed models as described above.

Multiple Imputation

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Data on walking speed over the follow-up were missing due to death, age>85 y, marked gait impairment, examination at home (where walking speed measures were not undertaken), and non-response. To investigate the influence of missing data, we used multiple imputation using surrogate measures of physical functioning (i.e., falls, disability) and measures associated with walking speed (e.g., MMSE, depressive symptoms) available for participants seen at home.

Missing values of walking speed were imputed based on the following covariates: all available walking speed measures, time, age, sex, education, height, BMI, hierarchical disability index, fall in the preceding year, MMSE score, depressive symptoms, and physical activity. No imputation was undertaken in those >85 years or excluded due to conditions associated with gait impairment, and after death. Twenty imputed data sets were generated using Proc MI and the estimates from the models were pooled using Proc MIANALYZE.

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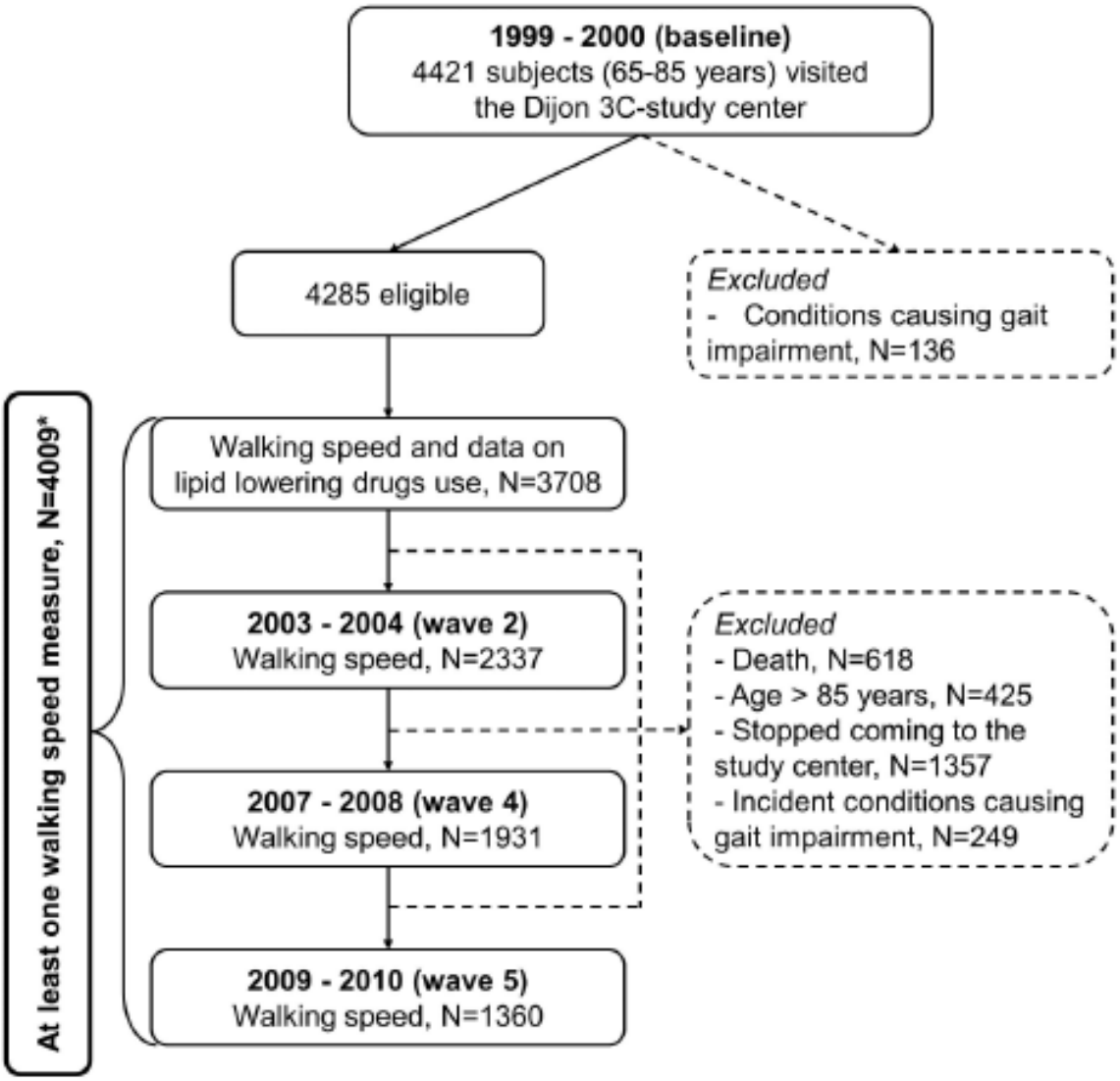
Supplementary figure. Flowchart of the study



*301 subjects had at least one measure of walking during follow-up but not at baseline.

Supplementary table 1. Association between use of LLDs at baseline (statins or fibrates) and change in fast walking speed (in cm/s) over the follow-up

	Model 1		Model 2		Model 3	
Change in fast walking speed	**Estimate (95% CI)**	***P* Value**	**Estimate (95% CI)**	***P* Value**	**Estimate (95% CI)**	***P* Value**
Time (y)	-2.18 (-2.37 to -2.00)	<0.001	-2.45 (-2.83 to -2.07)	<0.001	-2.60 (-3.08 to -2.13)	<0.001
Age at baseline x Time	-0.06 (-0.09 to -0.02)	<0.001	-0.07 (-0.10 to -0.03)	<0.001	-0.07 (-0.10 to 0.04)	<0.001
Sex (men *vs* women) x Time	-0.27 (-0.54 to 0.00)	0.050	0.25 (-0.12 to 0.63)	0.17	0.17 (-0.22 to 0.56)	0.38
LLDs use at baseline x Time						
No x Time	Reference	—	Reference	—	Reference	—
Statins x Time	0.59 (0.25 to 0.94)	<0.001	0.62 (0.28 to 0.97)	<0.001	0.67 (0.31 to 1.02)	<0.001
Fibrates x Time	0.48 (0.13 to 0.82)	0.007	0.44 (0.07 to 0.81)	0.021	0.48 (0.10 to 0.86)	0.009
LDL-cholesterol x Time	0.12 (-0.04 to 0.27)	0.13	0.07 (-0.08 to 0.22)	0.38	0.04 (-0.12 to 0.20)	0.61
HDL-cholesterol x Time	0.25 (-0.13 to 0.62)	0.19	0.08 (-0.30 to 0.46)	0.68	0.12 (-0.27 to 0.51)	0.55
Triglycerides (log) x Time	-0.21 (-0.57 to 0.16)	0.27	-0.14 (-0.52 to 0.23)	0.44	-0.16 (-0.55 to 0.22)	0.41

Continuous variables (age, LDL- and HDL-cholesterol, height, BMI, homocysteine, MMSE) were centered at their population mean; the reference groups for categorical variables were: baccalaureate degree; physically active; less than 20 pack-years of smoking; no alcohol consumption; no history of hypertension, diabetes mellitus, depression, coronary disease or peripheral artery disease; no use of NSAIDs, aspirin or psychotropic drugs.
Model 1: Mixed model adjusted for age, sex, LLDs use, baseline levels of cholesterol and triglycerides, and their interactions with time.
Model 2: Model 1 + baseline height, BMI, education level, hypertension, diabetes mellitus, coronary disease, use of psychotropic drugs or aspirin, level of homocysteine, and their interactions with time.
Model 3: Model 2 + baseline depressive symptoms, MMSE, physical activity, alcohol, smoking, peripheral artery disease, use of NSAIDs, and their interactions with time.

Supplementary table 2. Association between use of LLDs use over the follow-up (modelled at time-dependent variabls) and change in fast walking speed (in cm/s) over the follow-up

	Model 1		**Model 2**		**Model 3**	
Change in fast walking speed	**Estimate (95% CI)**	***P* Value**	**Estimate (95% CI)**	***P* Value**	**Estimate (95% CI)**	***P* Value**
Time (y)	-2.10 (-2.29 to -1.92)	<0.001	-2.22 (-3.21 to -1.23)	<0.001	-2.27 (-3.71 to -0.83)	0.002
Age at baseline x Time	-0.06 (-0.09 to -0.02)	<0.001	-0.07 (-0.14 to -0.01)	0.03	-0.04 (-0.11 to 0.03)	0.28
Sex (men *vs* women) x Time	-0.28 (-0.54 to -0.01)	0.04	0.12 (-0.71 to 0.95)	0.78	0.31 (-0.58 to 1.20)	0.50
Time-dependant LLDs use x Time	0.30 (0.04 to 0.56)	0.02	0.90 (0.28 to 1.51)	0.004	0.88 (0.26 to 1.51)	0.006
LDL-cholesterol x Time	0.07 (-0.08 to 0.23)	0.34	0.07 (-0.27 to 0.42)	0.68	0.12 (-0.24 to 0.47)	0.52
HDL-cholesterol x Time	0.24 (-0.13 to 0.61)	0.20	0.34 (-0.50 to 1.17)	0.43	0.41 (-0.44 to 1.26)	0.34
Triglycerides (log) x Time	-0.19 (-0.55 to 0.17)	0.30	0.38 (-0.40 to 1.16)	0.34	0.54 (-0.27 to 1.34)	0.19

Continuous variables (age, LDL- and HDL-cholesterol, height, BMI, homocysteine, MMSE) were centered at their population mean; the reference groups for categorical variables were: baccalaureate degree; physically active; less than 20 pack-years of smoking; no alcohol consumption; no history of hypertension, diabetes mellitus, depression, coronary disease or peripheral artery disease; no use of NSAIDs, aspirin or psychotropic drugs.
Model 1: Mixed model adjusted for baseline covariates (age, sex, levels of cholesterol and triglycerides) and time-dependent LLDs use, and their interactions with time.
Model 2: Model 1 + baseline (height, education level, homocysteine level) and time-dependent (LLDs use, BMI, hypertension, diabetes mellitus, coronary artery disease, use of psychotropic drugs and aspirin) covariates, and their interactions with time.
Model 3: Model 2 and time-dependent (depressive symptoms, MMSE, physical activity, alcohol, smoking, peripheral artery disease, use of NSAIDs), and their interactions with time.

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Supplementary table 3. Baseline characteristics of participants included in the analysis based on propensity scores

	Use of LLDs at baseline		
Baseline characteristics	**No (N=1116)**	**Yes (N=1116)**	***P* Value***
Age, years, mean (SD)	73.3 (4.7)	73.2 (4.4)	0.52
Women, n (%)	690 (61.8)	714 (63.9)	0.29
BMI, kg/m^2, mean (SD)	25.9 (4.2)	25.9 (3.9)	0.94
Height, cm, mean (SD)	161.7 (8.8)	161.1 (8.3)	0.10
Primary school or less, n (%)	729 (65.3)	736 (65.9)	0.82
Depressive symptoms, n (%)	144 (12.9)	134 (12.0)	0.52
MMSE, mean (SD)	27.4 (1.9)	27.4 (1.9)	0.98
Low physical activity, n (%)	248 (22.2)	243 (21.8)	0.80
Current drinker, n (%)	883 (79.1)	886 (79.4)	0.98
Hypertension, n (%)	916 (82.2)	915 (82.0)	0.96
Diabetes mellitus, n (%)	114 (10.2)	119 (10.7)	0.73
LDL-cholesterol, mmol/L, mean (SD)	3.45 (0.82)	3.40 (0.79)	0.16
HDL-cholesterol, mmol/L, mean (SD)	1.64 (0.41)	1.64 (0.40)	0.94
Triglycerides (log), mmol/L, mean (SD)	0.10 (0.40)	0.08 (0.42)	0.18

* Chi-square test or Student's test.

Supplementary table 4. Association between use of LLDs at baseline and change in fast walking speed over the follow-up: analysis based on propensity scores

	Model 1		Model 2		Model 3	
Change in fast walking speed	**Estimate (95% CI)**	***P* Value**	**Estimate (95% CI)**	***P* Value**	**Estimate (95% CI)**	***P* Value**
Time (y)	-1.88 (-2.29 to -1.48)	<0.001	-2.02 (-2.83 to -1.21)	<0.001	-2.14 (-3.10 to -1.19)	<0.001
Age x Time	-0.03 (-0.09 to 0.03)	0.32	-0.04 (-0.10 to 0.02)	0.20	-0.06 (-0.12 to 0.01)	0.07
Sex (men *vs* women) x Time	-0.64 (-1.18 to -0.10)	0.02	-0.28 (-1.01 to 0.42)	0.45	-0.40 (-1.15 to 0.35)	0.30
Baseline LLDs use x Time	0.52 (0.03 to 1.01)	0.03	0.53 (0.04 to 1.02)	0.03	0.57 (0.08 to 1.06)	0.02
LDL-cholesterol x Time	0.12 (-0.19 to 0.43)	0.45	0.07 (-0.24 to 0.38)	0.65	0.08 (-0.23 to 0.39)	0.61
HDL-cholesterol x Time	-0.16 (-0.91 to 0.60)	0.68	-0.23 (-0.98 to 0.52)	0.54	-0.30 (-1.06 to 0.46)	0.44
Triglycerides x Time	-0.48 (-1.20 to 0.23)	0.19	-0.49 (-1.21 to 0.23)	0.18	-0.51 (-1.23 to 0.21)	0.17

Continuous variables (age, LDL- and HDL-cholesterol, height, BMI, homocysteine, MMSE) were centered at their population mean; the reference groups for categorical variables were: baccalaureate degree; physically active; less than 20 pack-years of smoking; no alcohol consumption; no history of hypertension, diabetes mellitus, depression, coronary disease or peripheral artery disease; no use of NSAIDs, aspirin or psychotropic drugs.
Model 1: Mixed model adjusted for age, sex, LLDs use, baseline levels of cholesterol and triglycerides, and their interactions with time.
Model 2: Model 1 + baseline height, BMI, education level, hypertension, diabetes mellitus, coronary disease, use of psychotropic drugs or aspirin, level of homocysteine, and their interactions with time.
Model 3: Model 2 + baseline depressive symptoms, MMSE, physical activity, alcohol, smoking, peripheral artery disease, use of NSAIDs, and their interactions with time.

Supplementary table 5. Association between baseline use of LLDs use and change in fast walking speed (in cm/s) over the follow-up: analyses based on multiple imputation of missing values

	Model 1		Model 2		Model 3	
Change in fast walking speed	**Estimate (SE)**	***P* Value**	**Estimate (SE)**	***P* Value**	**Estimate (SE)**	***P* Value**
Time (y)	-2.29 (-2.47 to -2.10)	<0.001	-2.51 (-2.85 to -2.17)	<0.001	-2.58 (-3.00 to -2.13)	<0.001
Age x Time	-0.08 (-0.12 to -0.04)	<0.001	-0.09 (-0.13 to -0.05)	<0.001	-0.08 (-0.12 to -0.04)	<0.001
Sex (men *vs* women) x Time	-0.31 (-0.58 to -0.04)	0.03	0.15 (-0.22 to 0.52)	0.44	0.12 (-0.25 to 0.49)	0.52
Baseline LLD use x Time	0.31 (0.06 to 0.56)	0.01	0.31 (0.06 to 0.56)	0.02	0.32 (0.07 to 0.57)	0.01
LDL-cholesterol x Time	0.08 (-0.06 to 0.22)	0.26	0.05 (-0.09 to 0.19)	0.53	0.02 (-0.12 to 0.16)	0.75
HDL-cholesterol x Time	0.28 (-0.09 to 0.65)	0.16	0.06 (-0.31 to 0.43)	0.74	0.10 (-0.29 to 0.49)	0.62
Triglycerides (log) x Time	-0.14 (-0.49 to 0.21)	0.45	-0.05 (-0.40 to 0.30)	0.80	-0.06 (-0.43 to 0.31)	0.75

Continuous variables (age, LDL- and HDL-cholesterol, height, BMI, homocysteine, MMSE) were centered at their population mean; the reference groups for categorical variables were: baccalaureate degree; physically active; less than 20 pack-years of smoking; no alcohol consumption; no history of hypertension, diabetes mellitus, depression, coronary disease or peripheral artery disease; no use of NSAIDs, aspirin or psychotropic drugs.
Model 1: Mixed model adjusted for baseline covariates (age, sex, levels of cholesterol and triglycerides), and their interactions with time.
Model 2: Model 1 + baseline (height, education level, homocysteine level) and time-dependent (hypertension, diabetes mellitus, coronary artery disease, use of psychotropic drugs and aspirin) covariates, and their interactions with time.
Model 3: Model 2 + baseline (physical activity, depressive symptoms) and time-dependent (MMSE score, alcohol, smoking, use of NSAIDs) covariates, and their interactions with time.

Supplementary References

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