Disability and incident coronary heart disease in older community-dwelling adults: the Three-City Study.

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AUTHOR INFORMATION PAGE

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TITLE PAGE

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ABSTRACT

Context: Disability is a common condition in the elderly and has been associated with prevalent coronary heart disease (CHD) and with shorter longevity. However, whether disability predicts the occurrence of CHD has been less studied.

Objective: To prospectively assess the association between disability and incident fatal and non-fatal CHD among older adults free of cardiovascular disease (CVD).

Design and Settings: The Three-City (3C) Study is a French multicentre prospective population-based cohort of 9294 elderly subjects (3469 men and 5645 women) aged 65 and over at baseline between 1999 to 2001 and followed-up during 6 years.

Participants: 7354 participants with no history of CVD and with available information on disability status. Disability was assessed at baseline with a three levels of a hierarchical scale : no disability, mild disability (mobility only), moderate or severe disability (mobility plus activities of daily living and/or instrumental activities of daily living).

Main Outcome Measure: Incident fatal and non-fatal coronary events (angina pectoris, myocardial infarction, revascularization procedures and CHD death).

Results: At baseline, the mean level of the risk factors increased gradually with the severity of disability. After a median follow-up of 5.2 years, 264 first coronary events including 55 fatal events occurred. Participants with moderate or severe disability had a 1.8-fold (95%CI: 1.1-2.9) increased risk of overall CHD compared to non-disabled subjects in multivariate analysis, while those with mild disability were not at increased CHD risk. The association was found for fatal CHD only, for which the risk increased gradually with the severity of disability (mild disability: HR = 1.8, 95%CI: 0.9-3.8; moderate/severe disability: HR = 4.5, 95%CI: 1.8-11.3; p for trend = 0.002).

Conclusion: These data suggest that the association of disability with incident CHD is mostly due to an association with fatal CHD in community-dwelling elderly subjects.

TEXT

Coronary heart disease (CHD) is a leading cause of death in the elderly and in the face of population ageing in Western countries, assessment of individuals at increased risk of CHD is a major challenge for prevention [1]. Disability is a common condition in the elderly and has been associated with prevalent CHD [2; 3] and with shorter longevity [4-6]. However, whether disability is associated with the occurrence of CHD has been much less studied. The observation that disability increases CHD risk would suggest that disability is related to atherosclerosis development. Alternatively, disability might be a factor that impedes the prognosis of a coronary event independently of the atherosclerositc process. To date, only one study has explored the longitudinal association between disability and CHD in older persons [7]. This study found that disability was associated with a two-fold increased risk of CHD mortality in both genders, and to a lesser extent with the occurrence of CHD in women. However the possible confounding effect of prevalent cardiovascular disease (CVD) was not adequately taken into account by this study, and furthermore the spectrum of disability assessed was limited.

Our aim was therefore to assess prospectively the association of a large spectrum of disability levels with well-characterized incident fatal and non-fatal CHD events among non-institutionalized and CVD-free older adults from the Three-City Study.

Methods

Population

The Three-City Study is a French multicentre prospective study investigating the determinants of coronary heart disease, stroke and dementia in community-dwelling elderly. Details of the protocol have been previously described [8]. Briefly, community-dwellers aged 65 years and over were selected from the electoral rolls of

three large cities and then invited to participate in the study. Overall, 9294 subjects (3649 men and 5645 women) agreed to participate in the study, including 2104 from Bordeaux (South-West), 4931 from Dijon (North-East) and 2259 from Montpellier (South). The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre. Each participant signed an informed consent.

Baseline Data Collection

Trained interviewers conducted face-to-face interviews, using a standardized questionnaire. A wide range of information was collected including demographic characteristics, educational level, occupation, daily life habits such as smoking and alcohol consumption, functional status, cognitive testing, depressive symptoms, and the number of medications taken.

Depressive symptoms were evaluated with the Center for Epidemiologic Studies Depression Scale (CES-D) questionnaire, using a total score ≥ 23 in women and ≥ 17 in men as the cut-off value. Global cognitive functioning was assessed with the Mini Mental State Examination (MMSE) [9]. Past history of cardiovascular disease included history of coronary heart disease (angina pectoris, myocardial infarction or revascularization procedure), heart failure, stroke, surgery for lower limbs arteritis, abdominal aorta aneurysm and carotid arteries.

Participants underwent a standardized physical examination and were also invited to bring to the study centre all medications they have regularly used in the past month. Blood was collected following overnight fasting and centralized standard measurements of lipids and glucose levels were performed. Low-density lipoprotein cholesterol was calculated according to the Friedewald formula for triglycerides values ≤ 4.5 g/l only. Diabetes was defined as a fasting blood glucose level ≥ 7 mmol/l and/or treatment for diabetes. The body mass index (BMI) was calculated as

declared or measured weight (kg) divided by height (m) squared. Brachial blood pressure was measured twice after at least 5 minutes of rest in a seated position, with an appropriately sized cuff placed on the right arm, using a validated digital electronic tensiometer (OMRON M4, OMRON Corp., Kyoto, Japan). The mean blood pressure was then estimated. High blood pressure was defined as a mean systolic blood pressure (SBP) ≥ 140 mmgHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg. Participants who had either high blood pressure and/or who were treated for hypertension were considered hypertensive. Finally, 6631 subjects under 85 years underwent a bilateral ultrasound examination of the carotid arteries (common carotid arteries (CCA), the carotid bifurcations, and the origin of the internal carotid arteries) to assess the presence of plaques and intima-media thickness at the CCA (IMT), as previously described [10].

Assessment of disability

Three domains of disability were considered (table 1). Disability in mobility was assessed by the Rosow scale [11] which evaluates the ability to perform three activities (doing heavy housework, walking half a kilometre, and going up and down stairs). Instrumental activities of daily living (IADL) were evaluated using the Lawton scale [12] based on five items for men (ability to use the telephone, shopping, use of transportation, responsibility in taking medication, ability to handle finances) plus three additional items for women (doing laundry, housekeeping and food preparation). Disability in activities of daily living (ADL) was assessed by 5 items of the Katz scale [13] : bathing, dressing, toileting, transferring, and eating. Participants were considered disabled for one domain of disability if they needed help to perform at least one task at least of the domain assessed.

The disability status of the participants was thereafter classified according to a validated hierarchical disability scale in four categories [14] : no disability, mild disability (mobility disability only), moderate disability (mobility + IADL disability) and severe disability (mobility + IADL + ADL disability). In this Guttman scale, the 3 domains of disability are assumed to be successively (mobility then IADL then ADL) and cumulatively (an individual who is disabled for a given domain is also disabled for domains of lower rank-order) impaired during the disablement process (figure 1). Preliminary analysis indicates that this scale fitted 98.8% of the subjects in the current study and had almost perfect Guttman scalability [15], with a coefficient of reproducibility (CR) and a coefficient of scalability (CS) of 0.991 (95% CI 0.990-0.993) and of 0.983 (95% CI 0.980-0.986) respectively (95% CIs were estimated by 1000 bootstrap replications). The CR quantifies how a scale approximates a perfect Guttman scale and the CS determines the ability of the scale to rank individuals along the levels of difficulty. A CR value ≥ 0.90 and a CS value ≥ 0.60 are considered acceptable [15].

In the present study, since there were only 1.3% subjects with ADL disability, moderate and severe disability were combined, so that participants were finally classified as having no disability, mild disability (mobility disability only), and moderate or severe disability (mobility disability plus IADL and/or ADL disability).

Of the 9294 participants, 314 (3.4%) had no information on disability status. These latter were older (74.8 vs 73.8 y, p=0.003), had a lower MMSE-Score (26.8 vs 27.3, p=0.01) and had a slightly higher BMI (26.1 vs 25.5, p=0.01) compared to the 8980 subjects without missing data.

Because disability might be associated with the presence and/or a past history of CVD [2; 3], we further excluded 1626 subjects (18%) who had a past history of CVD defined below, leaving a final study population of 7354 subjects (figure 2).

Follow-up and events ascertainment

The study participants were re-evaluated at the study centre every 2 years during the first 4 years of follow-up. During these intermediate evaluations, subjects were interviewed about the hospitalisation for a coronary heart disease event in the past 2 years. For those who could not come to the study centre, a short standardized questionnaire was sent, that sought information on health events in the past 2 years, including coronary heart disease. Between 4 and 6 years of follow-up, CHD events were ascertained by contacting participants annually during 2 years (either by a self-administered questionnaire or by a telephone interview). For all subjects reporting a possible event, clinical information was sought directly from hospital or general practitioner records and validated by an independent expert committee. Coronary heart disease was defined as a hospitalized angina pectoris, a hospitalized myocardial infarction, a CHD death (I210-I219, I251-I259, I461 and R960 ICD-10 codes), or a revascularization procedure (percutaneous intervention or coronary artery bypass-grafting). For the 39 subjects who had several CHD events during follow-up, only the first one was considered for analysis. Moreover, among the 7354 participants who were free of CVD at baseline, 244 (3.3%) were lost to follow-up regarding CHD event ascertainment. These subjects were older, had a lower MMSE-Score, were more likely to be diabetic, were less treated for dyslipidemia and were more disabled than the remaining study participants (no disability: 34.4% vs 56.2% ;

mild disability: 39% vs 37% and moderate/severe disability: 27% vs 7%, $p < 0.0001$ after adjustment for age, gender and study centre).

Statistical analysis

Baseline characteristics according to the degree of disability were compared using multinomial logistic regression models, with adjustment for age, gender and study centre. Cumulative crude CHD incidence rate by baseline disability level was computed by the Kaplan-Meier product limit-method and compared using the Log Rank test. The hazard ratios (HRs) and 95% confidence intervals (95% CI) of mild disability and moderate/severe disability for CHD risk were estimated by Cox proportional hazard model taking no disability as the reference category. Three consecutive Cox models were built on an a priori basis: the first model included age, sex and study centre as covariates; the second model further included smoking status, daily alcohol consumption, BMI, diabetes, LDL and HDL cholesterol, hypertension and treatment for dyslipidemia; the third model additionally comprised educational level, income, household, the number of medications taken daily, MMSE-Score and depressive symptoms as covariates. Potential interactions between disability, pre-defined factors (age, gender, BMI and MMSE-score) and CHD risk were tested by entering product interaction terms in the fully adjusted Cox model. The proportional hazards assumption of the Cox model was checked for all covariates using Schoenfeld residuals. All analyses were two-sided and p values <0.05 indicated statistical significance. Statistical analysis were performed on SAS, version 9.1 (Cary, North Carolina, USA) and R, version 2.7.1 [16].

Results

Baseline characteristics

The study sample consisted of 7354 study participants (64% women) with full information on disability status and who were free of CVD at baseline, with a mean (SD) age of 73.8 years (5.4). Overall, 36.9% and 7.6% had mild and moderate/severe disability respectively. Their mean baseline characteristics are shown in table 2. Higher degree of disability was found in the older and in women. After adjustment for age, gender and study centre, disability was associated with lower socioeconomic status, lower lipid-lowering drugs use and lower MMSE score, the presence of diabetes and depressive symptoms, and the number of medications taken daily. Carotid intima-media thickness and carotid plaques did not differ between the groups.

Disability and first CHD events

After a median follow-up of 5.2 years, 264 first coronary events occurred of which 55 were fatal, yielding an estimated CHD incidence rate of 764.5 (95% CI: 672.2-856.7) for 100 000 person-years. As shown in figure 3, crude CHD incidence rate increased gradually with the baseline level of disability (p log-rank < 0.001). This association was found for fatal CHD events, but not for non fatal CHD events (figures 4A-4B).

The same pattern of association was found in multivariate analysis (table 3). Subjects with moderate/severe disability had a 2.2-fold (95% CI: 1.4-3.3) increased risk of overall CHD (i.e. fatal and non fatal) compared to subjects with no disability, after adjustment for age, sex and study centre. This relationship was slightly diminished in the fully adjusted model (HR=1.8; 95% CI: 1.1-2.9). In contrast, subjects with mild disability were not at increased CHD risk.

More specifically and after full adjustment (model 3), the risk of fatal CHD increased gradually with the severity of disability (mild disability: HR = 1.8, 95% CI: 0.9-3.8;

moderate/severe disability: HR = 4.5, 95%CI: 1.8-11.3; p for trend = 0.002), contrasting with the lack of association between disability and non fatal CHD.

The patterns of associations between disability and overall CHD risk on the one hand, and fatal CHD risk on the other hand, remained consistent in subgroup analysis by age, gender, BMI and MMSE-score, without any statistically significant interactions (all p values > 0.30 ; data not shown).

Discussion

In this large population based prospective study of community-dwelling and cardiovascular disease free elderly, disability was associated with a nearly 2-fold increased risk of overall CHD (i.e. fatal and non fatal) over 6 years. More specifically, the risk of fatal CHD increased gradually with the severity of disability, independently of major cardiovascular risk factors and other potential confounding factors. In contrast, no association was found between disability and non fatal CHD.

To date, only one population-based study, the EPESE study, has specifically investigated the association of disability with CHD incidence in the elderly [7]. In this study of 4116 US citizens aged 71 years or more, mobility disability and mobility plus ADL disability were both associated with a two-fold increased risk of CHD mortality over 4 years compared to non-disabled subjects. In addition, these 2 levels of disability were related to a 50% increased risk of non- fatal CHD in women only.

Our current results between disability and CHD mortality are consistent with that previous study. In addition, the results of our study complement those of the previous study in several respects. We identified fatal CHD events not only through death certificates but also from hospital records, which limited a potential classification bias [17]. To minimize the possible confounding effect of prior CVD, we excluded subjects

with baseline CVD. We investigated not only mobility and ADL disability as in the EPESE study, but also IADL disability. This may potentially explain why we observed a gradient of CHD mortality risk with baseline level of disability, contrary to the previous study. Finally, our study took place in a country at lower risk of CHD, in a more recent period (early 2000's vs. late 80's) and covering a broader age range.

The lack of association between disability and non fatal CHD suggests that disability has little to do with the coronary disease process and in particular atherosclerosis development. Accordingly, we did not observe any difference in the baseline burden of atherosclerosis (as measured by the presence of carotid plaques and by IMT) between levels of disability. Echographic criteria and the state of stability of the examined carotid plaques may give more sensitive information but these data were not available in the current study. Conversely, the results of the present study suggest that disability, even of mild severity, has more to do with the prognosis of CHD. A number of hypotheses might be postulated. First, disability might be associated with higher severity of CHD. In a study by Vaccarino & al [18], disability in ADL prior to hospital admission was clearly associated with the severity of acute myocardial infarction as assessed by the Killip class, the presence of new Q-waves on the first ECG and a lower systolic blood pressure. Second, disabled subjects suffering from an acute event might be treated less aggressively. In this same previous study, care disparities between disabled and non-disabled subjects were observed both for drugs (aspirin, beta-blockers) and for revascularization procedures during hospitalization. A more recent study suggested that disability status was strongly associated with the receipt of quality health care in a broad range of diagnostic categories [19]. Unfortunately, we did not collect information either on the

severity of CHD or on in-hospital treatment. Third, disability could be a prognosis factor “per se” by limiting the ability of disabled subjects to cope when an acute event occurs, making them more likely to die. Such inability to cope with stressors could be an indicator of an underlying state of frailty [20]. Unfortunately there is no consensus definition for frailty [21]. We tried to address this question by adjusting for the number of medications taken daily and by arm circumference, and found consistent associations of disability with fatal CHD (data not shown).

Clinical implications

These data suggest that primary prevention of CHD is of primary importance in disabled community-dwelling elderly. In this population, the promotion of regular physical activity seems appropriate as physical activity has been associated with a reduced severity of acute coronary syndrome, reduced in-hospital mortality rates and improved short-term prognosis, and with reduced disability [22-24]. Furthermore, there is some evidence that the use of ACE inhibitors in functionally impaired elderly people could improve physical function and prevent deterioration in health-related quality of life, through their cardiovascular effects, and by acting on skeletal muscle [25].

The results of the current investigation should be interpreted with some limitations in mind. Residual confounding by occult prevalent CVD including heart failure cannot be ruled out. Analyses were based on a single measurement of disability at baseline. However, in elderly subjects, disability is more likely to worsen than to improve, so that our risk estimates were more likely to be conservative [26]. As community-dwelling volunteers, the present study participants may be less representative of the general elderly population, especially the frailest [8] and those in institutions.

Conclusion

In summary, the present study provides evidence that the association of disability with incident CHD is mostly due to an association with fatal CHD in community-dwelling elderly. This would suggest that disability is more likely a prognosis than a risk factor for CHD in the elderly. The mechanisms underlying this specific association are likely from multiple causes that remain to be further investigated. Current evidence suggests that promotion of physical activity in the elderly is appropriate to both reduce the severity of CHD in those who are disabled but also to prevent the onset of disability in the elderly.

References

1Aouba A, Péquignot F, Le Toullec A, Jougla E: **Medical causes of death in France in 2004 and trends 1980-2004**. *Bul Epidemiol Hebd* 2007, **35-36**:308-314.

2van Jaarsveld CH, Sanderman R, Miedema I, Ranchor AV, Kempen GI: **Changes in health-related quality of life in older patients with acute myocardial infarction or congestive heart failure: a prospective study**. *J Am Geriatr Soc* 2001, **49**:1052-1058.
3Pinsky JL, Jette AM, Branch LG, Kannel WB, Feinleib M: **The Framingham Disability Study: relationship of various coronary heart disease manifestations to disability in older persons living in the community**. *Am J Public Health* 1990, **80**:1363-1367.
4Corti MC, Guralnik JM, Salive ME, Sorkin JD: **Serum albumin level and physical disability as predictors of mortality in older persons**. *JAMA* 1994, **272**:1036-1042.
5Scott WK, Macera CA, Cornman CB, Sharpe PA: **Functional health status as a predictor of mortality in men and women over 65**. *J Clin Epidemiol* 1997, **50**:291-296.
6Fried LP, Kronmal RA, Newman AB, Bild DE, Mittelmark MB, Polak JF, Robbins, J A & Gardin, J M: **Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study**. *JAMA* 1998, **279**:585--592.
7Corti MC, Salive, M E & Guralnik, J M: **Serum albumin and physical function as predictors of coronary heart disease mortality and incidence in older persons**. *J Clin Epidemiol* 1996, **49**:519--526.
8The 3C Study Group: **Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population**. *Neuroepidemiology* 2003, **22**:316-325.
9Folstein MF, Folstein SE, McHugh PR: **"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician**. *J Psychiatr Res* 1975, **12**:189-198.
10 Zureik M, Gariépy J, Courbon D, Dartigues J, Ritchie K, Tzourio C, Alpérovitch A, Simon A, Ducimetière P: **Alcohol consumption and carotid artery structure in older French adults: the Three-City Study**. *Stroke* 2004, **35**:2770-2775.
11 Rosow I, Breslau N: **A Guttman health scale for the aged**. *J Gerontol* 1966, **21**:556-559.
12 Lawton MP, Brody EM: **Assessment of older people: self-maintaining and instrumental activities of daily living**. *Gerontologist* 1969, **9**:179-186.
13 Katz S, Downs TD, Cash HR, Grotz RC: **Progress in development of the index of ADL**. *Gerontologist* 1970, **10**:20-30.
14 Barberger-Gateau P, Rainville C, Letenneur, L & Dartigues, J F: **A hierarchical model of domains of disablement in the elderly: a longitudinal approach**. *Disabil Rehabil* 2000, **22**:308--317.
15 Dunn-Rankin P: *Scaling Methods*. Lawrence Erlbaum Associates; 1983.
16 R Development Core Team: **R: A Language and Environment for Statistical Computing**. , ; 2008.
17 Coady SA, Sorlie PD, Cooper LS, Folsom AR, Rosamond WD, Conwill DE: **Validation of death certificate diagnosis for coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study**. *J Clin Epidemiol* 2001, **54**:40-50.
18 Vaccarino V, Berkman LF, Mendes de Leon CF, Seeman TE, Horwitz RI, Krumholz HM: **Functional disability before myocardial infarction in the**

elderly as a determinant of infarction severity and postinfarction mortality. *Arch Intern Med* 1997, **157**:2196-2204.
19 Chan L, Ciol MA, Shumway-Cook A, Yorkston KM, Dudgeon BJ, Asch SM, Hoffman JM: **A longitudinal evaluation of persons with disabilities: does a longitudinal definition help define who receives necessary care?**. *Arch Phys Med Rehabil* 2008, **89**:1023-1030.
20 Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G: **Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care**. *J Gerontol A Biol Sci Med Sci* 2004, **59**:255-263.
21 Topinková E: **Aging, disability and frailty**. *Ann Nutr Metab* 2008, **52 Suppl 1**:6-11.
22 Pitsavos C, Kavouras SA, Panagiotakos DB, Arapi S, Anastasiou CA, Zombolos S, Stravopodis P, Mantas Y, Kogias Y, Antonoulas A, Stefanadis C: **Physical activity status and acute coronary syndromes survival The GREECS (Greek Study of Acute Coronary Syndromes) study**. *J Am Coll Cardiol* 2008, **51**:2034-2039.
23 Chakravarty EF, Hubert HB, Lingala VB, Fries JF: **Reduced disability and mortality among aging runners: a 21-year longitudinal study**. *Arch Intern Med* 2008, **168**:1638-1646.
24 Heath JM, Stuart MR: **Prescribing exercise for frail elders**. *J Am Board Fam Pract* 2002, **15**:218-228.
25 Sumukadas D, Witham MD, Struthers AD, McMurdo MET: **Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial**. *CMAJ* 2007, **177**:867-874.
26 Lamarca R, Ferrer M, Andersen PK, Liestol K, Keiding, Niels & Alonso, Jordi: **A changing relationship between disability and survival in the elderly population: differences by age**. *J Clin Epidemiol* 2003, **56**:1192--1201.

Table 1 : Domains of disability assessed at baseline. The Three-City Study.

Scale	Domain of disability	Activities
Rosow[11]	Mobility	- Doing heavy housework - Walking half a km - Going up/downstairs
Lawton[12]	Instrumental Activities of Daily Living	- Using the phone - Using public transportation - Shopping - Responsibility to take medication - Handling finances - Doing laundry (women only) - Housekeeping (women only) - Cooking (women only)
Katz[13]	Activities of Daily Living	- Bathing - Dressing - Toileting - Transferring - Eating

Figure 1: Disability Hierarchical Scale[14]. The Three-City Study.

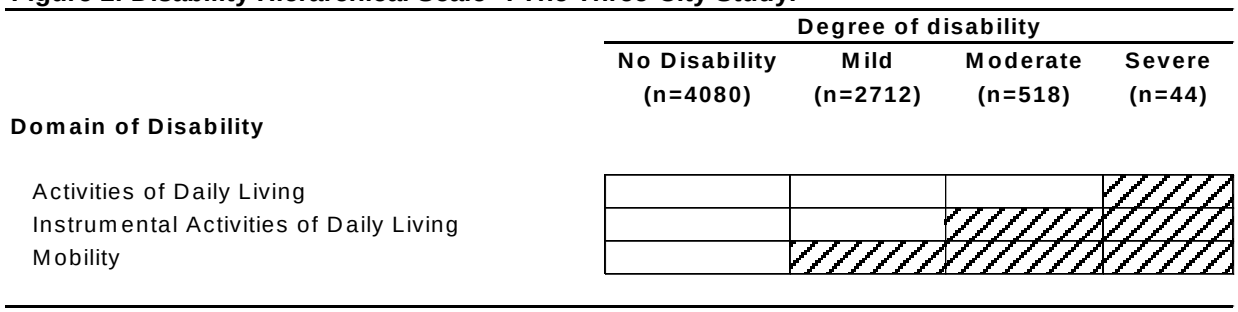
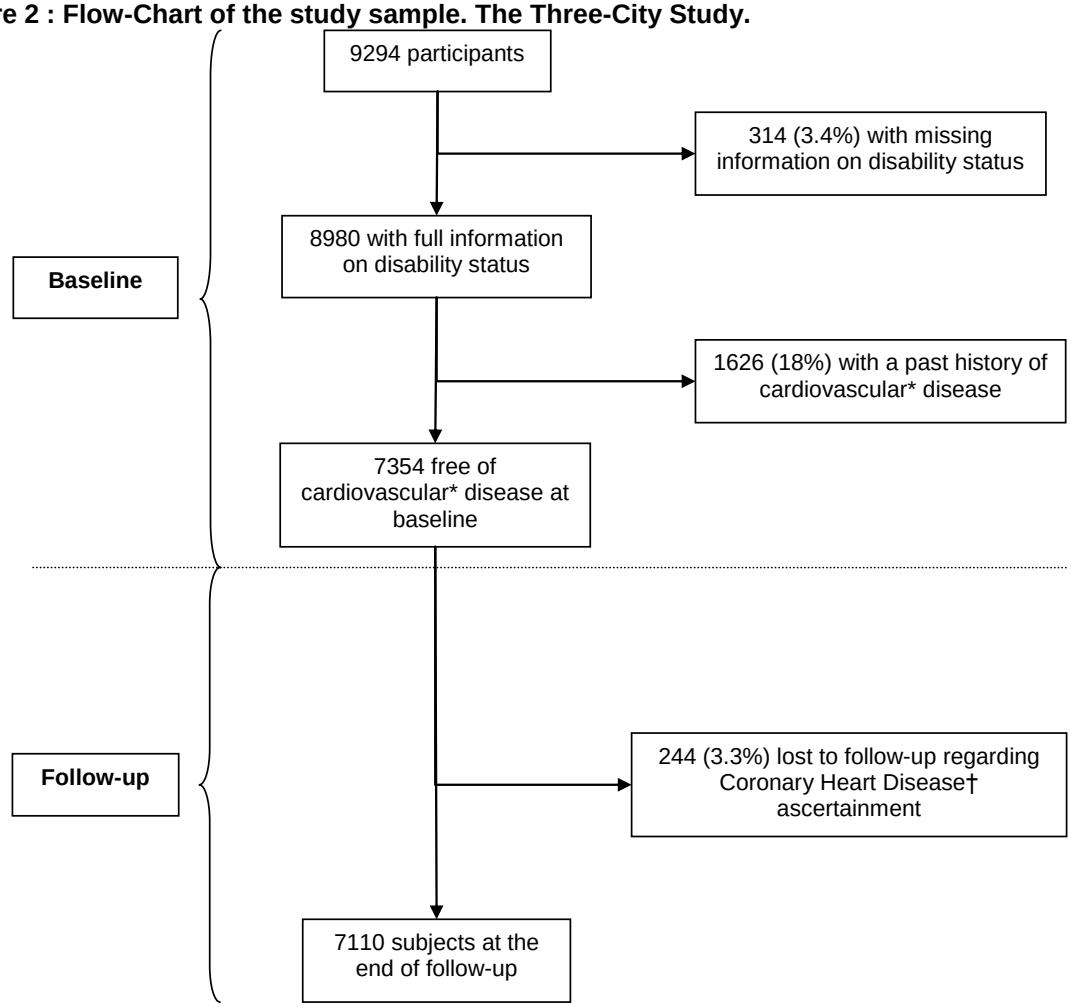


Figure 2 : Flow-Chart of the study sample. The Three-City Study.



* Cardiovascular disease is defined at baseline, by past history or presence of at least one of the following diseases: myocardial infarction, angina pectoris, revascularization procedure, stroke, heart failure, surgery for lower limbs arteritis, carotid artery surgery or surgery for abdominal aorta aneurysm.

† Coronary heart disease is defined by myocardial infarction, angina pectoris and revascularization procedure.

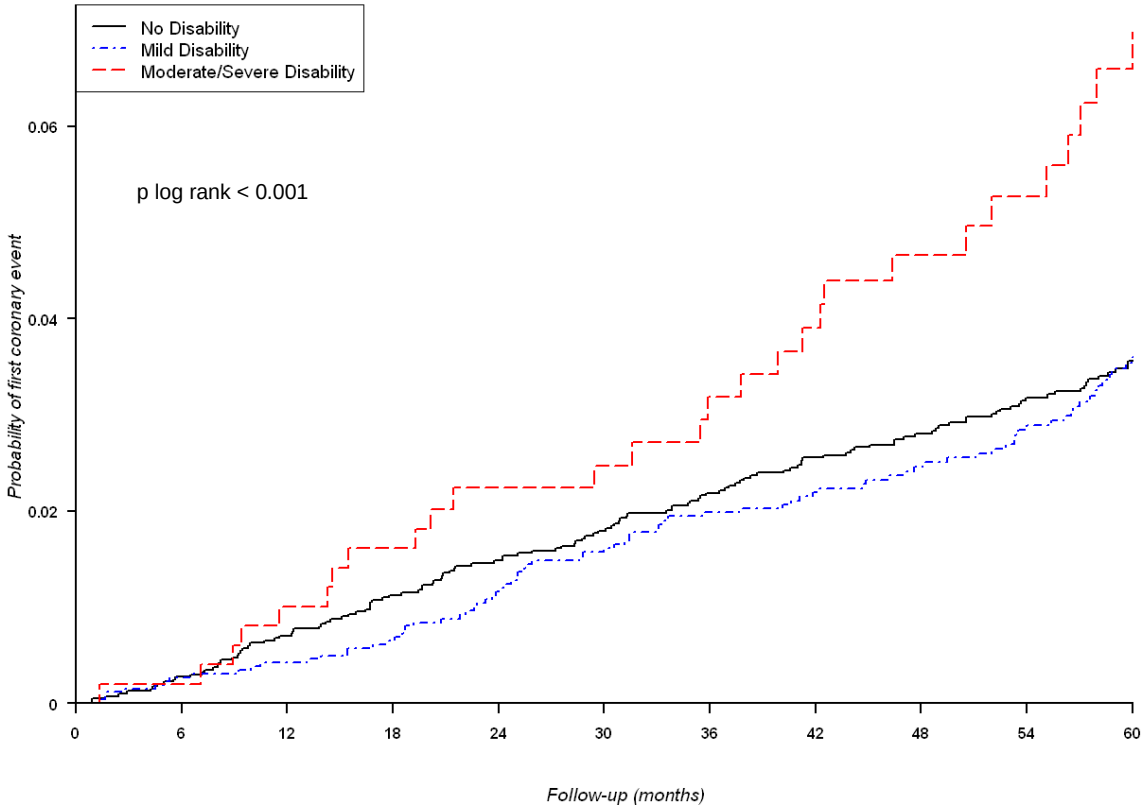
Table 2: Baseline characteristics by baseline level of disability. The Three-City Study (n=7354).

	Degree of disability			
	No disability (n=4080)	**Mild disability (n=2712)**	**Moderate or severe disability (n=562)**	**p-value***
Age (years)	72.1 (4.4)	75.4 (5.4)	79.0 (6.5)	-
Sex (Men)	44	25	23	-
Sociodemographic factors				
Level of education (Primary)	31	32	45	< 0.0001
Living alone	29	45	47	0.0005
Income (< 1500 €/month)	30	38	50	< 0.0001
Medical history				
BMI (kg/m²)	25.4 (3.7)	25.6 (4.3)	25.9 (5.2)	< 0.0001
Total Cholesterol (mmol/l)	5.88 (0.95)	5.88 (1.00)	5.92 (1.12)	0.002
LDLc (mmol/l)	3.70 (0.84)	3.65 (0.88)	3.69 (0.96)	0.0001
HDLc (mmol/l)	1.62 (0.39)	1.66 (0.42)	1.61 (0.43)	0.0004
Current smoker	6	6	4	0.40
Alcohol consumption (glasses/day)				
No alcohol	16	25	33	
< 3	48	48	45	< 0.0001
≥ 3	32	24	18	
Diabetes	8	9	11	< 0.0001
Hypertension	75	76	79	0.35
Treatment for dyslipidaemia	29	29	18	0.0002
Five drugs or more	33	52	66	< 0.0001
MMSE-Score	27.5 (1.9)	27.3 (2.1)	25.8 (3.4)	< 0.0001
Depressive symptoms†	8.8	17	26	< 0.0001
Carotid arteries parameters‡				
Intima-media thickness (mm)	0.71 (0.12)	0.71 (0.12)	0.73 (0.12)	0.39
Carotid plaques	40	46	51	0.73

Data are % and mean (SD) for categorical and continuous variables respectively.
* Multinomial logistic regression adjusted for age, gender and study centre.
† CES-D Score ≥ 23 for women and ≥ 17 for men
‡ Analysis restricted to subjects who underwent an ultrasound carotid examination(n = 6681).
BMI for Body Mass Index; LDLc for Low-Density Lipoprotein cholesterol; HDLc for High Density Lipoprotein cholesterol; MMSE for Mini-Mental State Examination

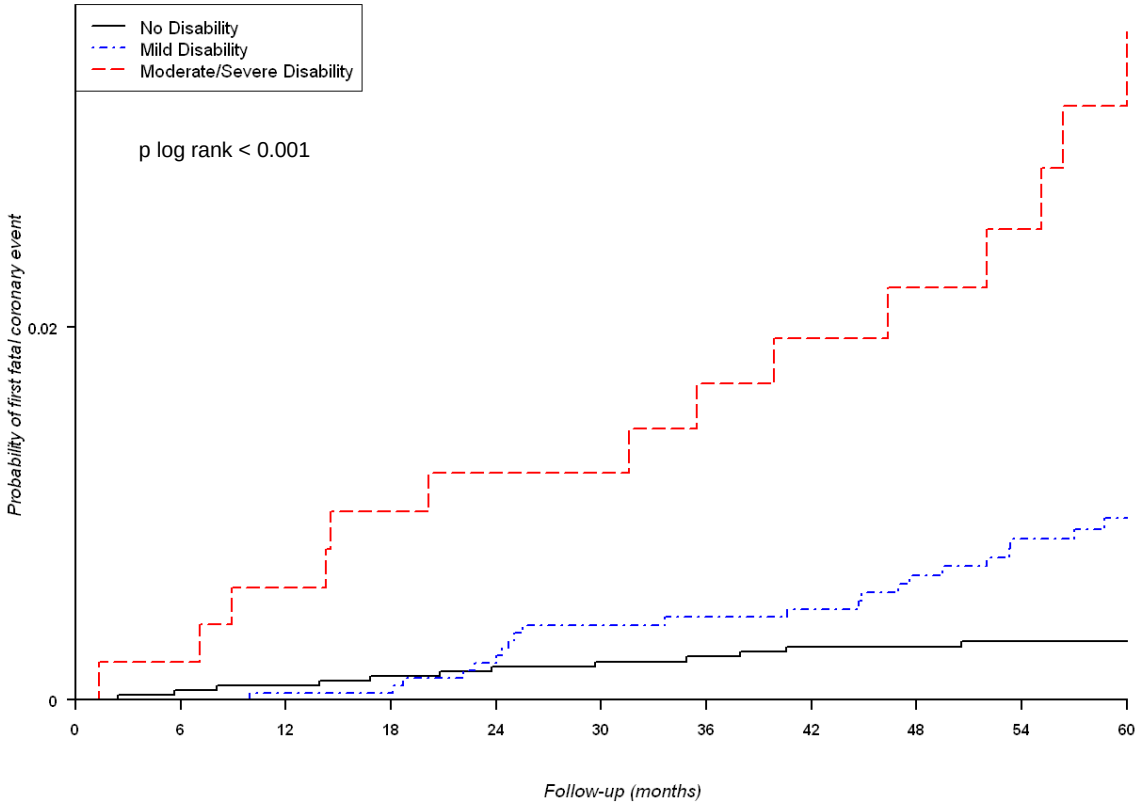
Mild disability : disability in mobility only
Moderate/severe disability : disability in mobility + ADL and/or IADL.

Figure 3: Unadjusted Kaplan-Meier cumulative probability of coronary heart disease according to baseline degree of disability. The Three-City Study.



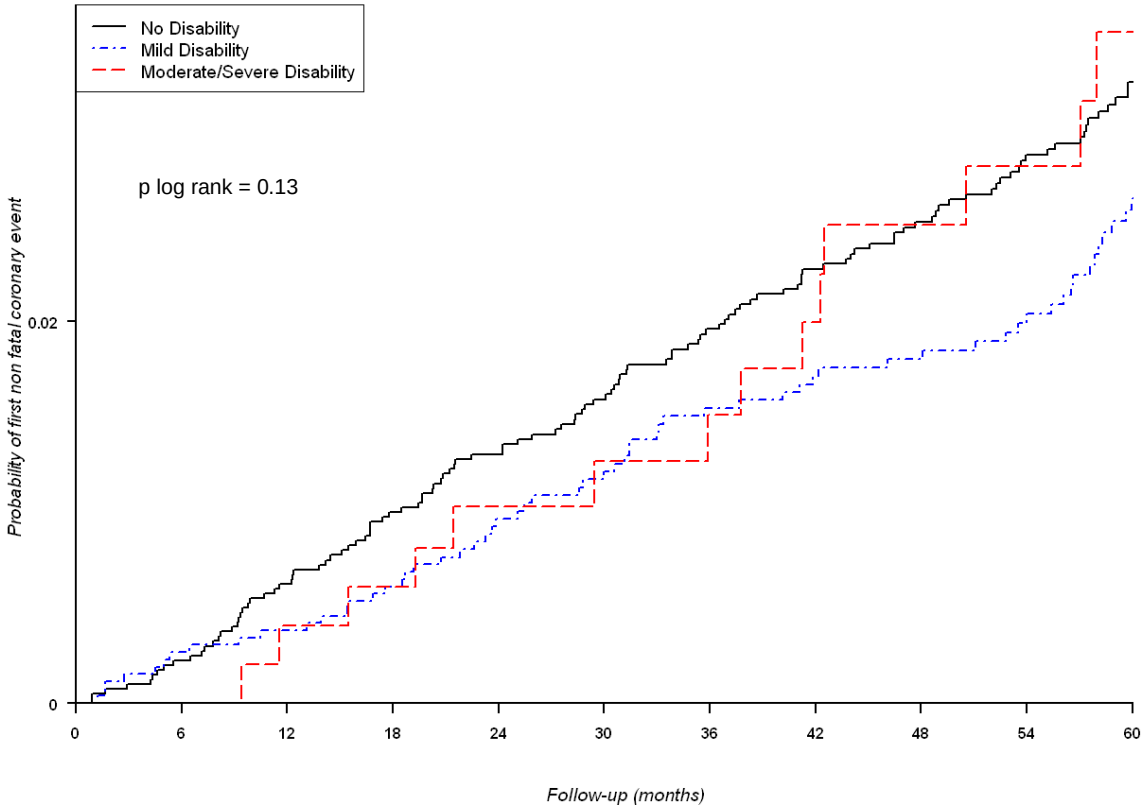
Mild disability : disability in mobility only (n = 2712).
Moderate/severe disability : disability in mobility + ADL and/or IADL (n = 562).

Figure 4A: Unadjusted Kaplan-Meier cumulative probability of fatal incident coronary heart disease according to baseline degree of disability. The Three-City Study.



Mild disability : disability in mobility only (n = 2712).
Moderate/severe disability : disability in mobility + ADL and/or IADL (n = 562).

Figure 4B: Unadjusted Kaplan-Meier cumulative probability of incident non-fatal coronary heart disease according to baseline degree of disability. The Three-City Study.



Mild disability : disability in mobility only (n = 2712).
Moderate/severe disability : disability in mobility + ADL and/or IADL (n = 562).

Table 3. Hazards ratios of disability for first coronary heart disease over 6 years of follow-up. The Three-City Study.

	Incident Coronary Heart Disease (n=264)			Incident Fatal Coronary Heart Disease (n=55)			Incident Non Fatal Coronary Heart Disease (n=209)		
	Events	HR	95% CI	Events	HR	95% CI	Events	HR	95% CI
Model 1									
No Disability (n=4080)	143	1.0	Ref.	15	1.0	Ref.	128	1.0	Ref.
Mild Disability (n=2712)	87	1.0	[0.8 - 1.3]	23	2.2	[1.1 - 4.4]	64	0.9	[0.6 - 1.2]
Moderate or severe disability (n=562)	34	2.2	[1.4 - 3.3]	17	8.0	[3.6 - 17.8]	17	1.3	[0.8 - 2.3]
p for trend			0.01			< 0.0001			0.87
Model 2									
No Disability (n=4080)	134	1.0	Ref.	15	1.0	Ref.	119	1.0	Ref.
Mild Disability (n=2712)	80	1.0	[0.7 - 1.3]	20	1.9	[0.9 - 4.0]	60	0.9	[0.6 - 1.2]
Moderate or severe disability (n=562)	29	2.0	[1.3 - 3.1]	13	5.9	[2.4 - 14.4]	16	1.3	[0.8 - 2.3]
p for trend			0.05			0.0002			0.85
Model 3									
No Disability (n=4080)	134	1.0	Ref.	15	1.0	Ref.	119	1.0	Ref.
Mild Disability (n=2712)	80	0.9	[0.7 - 1.3]	20	1.8	[0.9 - 3.8]	60	0.8	[0.6 - 1.1]
Moderate or severe disability (n=562)	29	1.8	[1.1 - 2.9]	13	4.5	[1.8 - 11.3]	16	1.3	[0.7 - 2.3]
p for trend			0.15			0.002			0.85

HR = Hazards ratio; 95% CI = 95% confidence interval; Hazards ratios and 95% CI were estimated by Cox proportional hazards models.

Mild disability: mobility disability only.
Moderate or severe disability: mobility disability plus IADL and/or ADL disability

Model 1 adjusted for age, sex, and centre.
Model 2 = Model 1 + BMI, current smoking, alcohol consumption, LDL and HDL cholesterol, hypertension, diabetes and treatment for dyslipidemia.
Model 3 = Model 2 + MMSE score, depressive symptoms , level of education, living status (alone or not alone), income and number of medications taken daily.