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Long-term Prognostic Impact of Physical Activity in Patients with Stable Coronary Heart Disease

Running Title: Physical activity benefits in stable coronary heart disease

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Abstract

Stable coronary heart disease (CHD) patients are advised to practice regular physical activity (PA). However, data on very long-term prognosis impact of regular exercise remain scarce. We aimed to evaluate the impact of physical activity level on mortality at long term in stable CHD patients. We analyzed 822 patients with stable CHD. They answered questionnaires on medical history, underwent a standardized clinical examination, and provided a fasting blood sample. PA was evaluated by the MOSPA questionnaire. Three tertiles of patients were individualized according to PA level: 0.0-9 Metabolic Equivalent of Task (METs) hour per week (n=267); 10-39.9 METs hour per week (n=279); and ≥ 40 METs hour per week (n=276). After a median follow-up of 14.6 years, 324 patients had died. In a multivariate analysis adjusted for age, dyslipidemia, smoking status, diabetes, high blood pressure, waist circumference, left ventricular ejection fraction, Gensini score, heart rate, ankle-brachial index and duration of disease, physical activity was significantly and independently associated with all-cause mortality. Compared to the lowest PA tertile, both the median and the highest PA tertiles, were associated to a reduction of all-cause mortality risk with HR at 0.79 (95%CI [0.61:1.03], p=0.08) and 0.71 ([0.53:0.96], p=0.025) respectively; p for trend =0.02. Adjusted HR for an increase of 10 METs hour per week was 0.95 [0.92-0.98], (p<0.002). In conclusion, our study demonstrates an independent association between PA and long term vital prognosis with a 5% total mortality decrease for an increase of 10 METs hour per week.

Keywords: Coronary Heart Disease; Prognosis; Physical activity

Current European guidelines for management of stable Coronary Heart Disease (CHD) patients recommend to practice a regular physical activity consisting of 30 min of moderate-to-vigorous intensity aerobic exercising, at least 3 times a week(1). American guidelines encourage CHD patients to practice 150 min per week of moderate intensity exercising, both for primary and secondary prevention (2, 3). Moreover, physical activity is part of cardiac rehabilitation programs which are demonstrated to reduce cardiovascular mortality and hospital admission in CHD patients (4, 5). However, although numerous publications focused on prognosis impact of physical activity in CHD patients, no study in the literature demonstrates the relation between physical activity level - assessed quantitatively by a validated method - and mortality, after complete adjustment on potential confounding factors in CHD on a very long term follow-up. We sought to analyze the relation between the level of physical activity, assessed by the MOSPA questionnaire, and long term all-cause mortality in a cohort of patients with known stable Coronary Heart Disease.

Methods

The Genetique et ENvironnement en Europe du Sud (GENES) study was designed to assess the role of gene-environment interactions in the occurrence of CHD(6-12). From 2001 to 2004, we prospectively recruited in this study 834 male patients aged between 45 and 74, living in the Toulouse area (South-western France), admitted in the Department of Cardiology of Toulouse University Hospital, and referred for evaluation and management of their stable CHD. Stable CHD was defined by a previous history of acute coronary syndrome, a previous history of coronary revascularization, a documented myocardial ischemia, a stable angina or the presence of a coronary stenosis of 50% or more at the coronary angiography. Patients who had presented an acute coronary episode during the past seven days were not included in the study, as they were considered as not stable. Those with a previous history of cancer were not included, as their life expectancy was potentially reduced due to their neoplasm.

The study protocol was approved by the local ethics committee (file # 1-99-48, 22/02/2000), in agreement with the French law on human biomedical research and the Declaration of Helsinki. All participants signed an informed consent attesting that they received all the information they needed about the study and that they agreed to participate.

Vital status (and date of death when applicable) was obtained on December 31st, 2017 for each participant through the French national database recording all deaths occurring in the French population. Our endpoint was all-cause mortality. Variables were collected through standardized face-to-face interviews and also checked in the patients' medical files. A physical examination was performed by a single physician using standard measurement methods.

Patients were considered as diabetics if they took oral antidiabetic drugs and/or insulin or if their blood glucose level was equal to or higher than 7 mmol/L (126 mg/dL). They were considered as having dyslipidemia if they took a lipid-lowering treatment or if LDL-cholesterol was 4.1 mmol/L (160 mg/dL) or above. Renal function was assessed using the Cockcroft and Gault formula. Severe chronic renal failure was defined by a glomerular filtration rate lower than 30 ml/min. Left Ventricular Ejection Fraction (LVEF) was assessed by ventriculography or by isotopic method or echocardiography when ventriculographic measurements were lacking. All patients underwent a coronary angiography. Coronary stenosis of 50% or more was considered significant. Diffusion of coronary heart disease lesions was assessed by calculating the Gensini Score (13). Detailed baseline assessment of net energy expenditure in relation with work, commuting and leisure time physical activity in the preceding year, according to category of activity, was obtained by the MONICA Optional Study of Physical Activity questionnaire, (MOSPA questionnaire) (14, 15). The MOSPA questionnaire is divided up into four activity categories: occupational, travel to work, household, and leisure-time physical activity. It aims to take in consideration the whole energy expenditure of the subject. Physical activity was expressed in weekly metabolic equivalent scores (MET) hour per week and for the present analysis, physical activity was

graduated in tertiles and our cohort was thus divided into three groups. All the data detailed above were collected at baseline only.

Statistical analysis was performed on STATA statistical software, release 14.1 (Stata Corporation, College Station, Texas, USA). Continuous variables were summarized as means and standard deviations. Categorical variables are presented as proportions. In univariate analysis, categorical variables were compared with *Chi²-test* (or *Fischer's exact test* when necessary). *ANOVA* were used to compare the distribution of continuous normally distributed data according to tertiles of physical activity. *Kruskal-Wallis tests* (or logarithmic transformation of the variable when necessary) were used when distribution departed from normality, or when homoscedasticity was rejected. A p-value < 0.05 was considered statistically significant.

Cumulative survival of patients was determined by the Kaplan-Meier method and compared using the *Log-rank test*. Univariate and multivariate Cox regression models were used to investigate the association between variables and mortality during the follow-up and to determine hazard ratios (HR) for mortality and 95% confidence intervals (95% CI). Regression analyses were performed with polynomial models (quadratic and cubic) to examine for possible non-linear relationships between continuous variables (especially physical activity) and mortality. All variables associated with a p-value < 0.20 in univariate analysis were introduced in a multivariate Cox model. A backward procedure was applied to assess variables that were significantly and independently associated with mortality (p-value < 0.05). However, cardiovascular risk factors (High Blood Pressure, diabetes, and dyslipidemia) were kept in the multivariate Cox analysis even if they were not significantly associated with mortality, given that these variables are well described prognostic factors in the literature. The proportional-hazard assumption was tested for each covariate by the "log-log" method, plotting $(-\ln[-\ln(\text{survival})])$ for each category of a nominal covariate, versus $\ln(\text{analysis time})$. None of the assumptions could be rejected.

Results

We prospectively included 834 men aged 45 to 74 years presenting with stable CHD. Final analysis was performed in 822 subjects with complete data. Vital status was obtained on December 31, 2017 for all patients. During the follow-up period, 324 patients died (39.4%). The median follow-up was 14.6 years. The 822 patients were divided in three tertile according to their level of physical activity. First tertile ranged from 0 to 9.9 METs hour per week, second from 10 to 39.9 METs hour per week and the third included patients with physical activity superior or equal to 40 METs hour per week. The baseline patients' characteristics according to their physical activity are listed in **Table 1**. At the end of the follow-up period, mortality rate was 46.1% in the lowest tertile, 23.4% in the median and 17.6% in the highest (log rank test, $p < 0.001$). The Kaplan-Meier survival curves, according to physical activity, are presented in **Figure a**. No interaction exists between physical activity and LVEF, however, we show for illustrative purpose in **Figure b** the association between all-cause mortality and level of physical activity. In the multivariate analysis, the Cox proportional hazard model was adjusted for age, dyslipidemia, smoking status, diabetes, high blood pressure, total cholesterol, waist circumference, left ventricular ejection fraction, Gensini score, heart rate, ankle-brachial index and duration of disease. Physical activity remained significantly and independently associated with a significant decrease in the risk of all-cause death. Compared to the first tertile (0 to 9.9 METs hour per week), both the second tertile (10 to 39.9 METs hour per week) and the third tertile (>40 METs hour per week) were associated to a reduction of all-cause mortality risk with HR at 0.79 (95%CI [0.61:1.03], $p=0.08$) and 0.71 ([0.53:0.96], $p=0.025$) respectively; p for trend =0.02 (**Table 2**). Adjusted hazard ratio for an increase of 10 METs hour per week was 0.95 [0.92-0.98], ($p<0.002$). The others independent predictors of all-cause mortality in our cohort were: age, waist circumference, heart rate, tobacco status, length of disease, ankle brachial index, LVEF, diabetes and dyslipidemia (**table 3**).

Discussion

In this study, based on a cohort of stable male CHD patients, we demonstrate the independent association between long term all-cause mortality and self-reported physical activity level assessed at inclusion by the MOSPA questionnaire.

Previous studies have addressed the issue of the impact of physical activity on stable CHD patients survival. In 2000, Wannamethee *et al*, reported results from a cohort of 722 male CHD patients showing that a light or moderate physical activity was associated with a lower risk of all-cause mortality(16). These results were limited by a relatively short follow-up of 5 years and were difficult to interpret, as physical activity was classified by type (walking, gardening, and sporting activity) without numerical quantification of energy expenditure. In 2006, another survey including 1,045 subjects with reported CHD, with a 9-year follow-up, outlined the inverse graded relation between physical activity and all-cause mortality(17). In this study, energy expenditure was quantified and the results were consistent for various strata of the cohort (sex, age, comorbid conditions...). However, this study focused on elderly patients (over 65) and adjustment in multivariate analysis does not include important variables such as left ventricular function and cardio-vascular risk factors. In 2008, Appullan *et al*, published data from the CASS Registry with a median follow-up of 14.7 years(18). Similarly to our study, their results demonstrated an independent correlation between the level of physical activity and long term mortality. These data are of interest as they derived from a very large population of 14,021 individuals. However, physical activity was not assessed accurately and was simply graded into four categories (sedentary, mild, moderate and strenuous). Moreover, these patients were recruited in the 1970s and 1980s and the advances made in the treatment of CHD since then are likely to attenuate the prognosis impact of physical activity. At last, the adjustment on potential confounding factors in CHD seems here again incomplete, as left ventricular function is missing. More recently, two large studies addressed the question of physical activity in CHD. In 2017, Stewart *et al* analyzed the data of a cohort of 15,486 patients from 39 countries with stable CHD followed over 3.7 years(19) included in the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of

Darapladib Therapy) trial. Physical Activity was estimated by a questionnaire that provided a quantitative assessment of physical activity in METS hour per week. This study showed that a higher level of physical activity was independently associated with lower all-cause mortality, especially in patients sedentary at baseline or in high risk patients, as estimated by the ABC-CHD risk score. These results are of interest, but the follow-up duration is limited. Moholdt *et al* published in 2018 a study with 3307 individuals who self-reported to suffer from CHD, with a median follow-up of 15.7 years(20). This work focused on the impact on mortality of physical activity and weight lost. It showed a significant mortality risk reduction associated with sustained physical activity and no mortality risk reduction associated with weight loss. The first limitation of that survey was the semi-quantitative assessment of physical activity (inactive, low activity, high activity). Other limitation is the lack of relevant cardiac data in CHD, such as LVEF, in order to provide a complete adjustment in multivariate analysis. Our study demonstrates the independent association between long term all-cause mortality and physical activity level, consistently with the previous reports listed above, with a long term follow-up, a complete adjustment on potential confounding factors in CHD and a quantitative assessment of energy expenditure.

This association between physical activity and long term all-cause mortality is also observed in our study in patients with reduced ejection fraction, as shown in **Figure b**. However, the benefit of physical activity on mortality in heart failure patients is still under debate. In 2019 a Cochrane review of 44 clinical trials evaluating exercise-based cardiac rehabilitation for heart failure patients concluded that it reduces short-term overall hospital admission (16.7% vs 23.7% RR=0.70 95%CI[0.60-0.83]); however no differences were observed regarding all-cause mortality at 1-year follow-up between patients that benefited from cardiac rehabilitation and controls, although a tendency appeared in long term follow-up (>1 year) : 17.2% vs 19.6%, RR=0.88 95%CI[0.75-1.02](21). It is noteworthy that the population this Cochrane review is a combination of patients presenting with different heart failure etiology (not only ischemic), and different levels of LVEF (preserved and reduced LVEF). Moreover, few of the

studies included in this meta-analysis had a long term follow-up. In 2012, Belardinelli *et al* published a report with a 10-year follow-up, based on patients with depressed LVEF (mean LVEF 37%), 80% of whom had ischemic etiology: a significant benefit of moderate physical activity on mortality was observed (HR=0.68 95%CI[0.30-0.82] (22). These data, resulting from a population comparable to the patients with depressed LVEF of our cohort, are consistent with our results.

Our study presents some limitations. First, physical activity level was self-evaluated based on a questionnaire. Although this method is robust, it remains less accurate than direct assessment methods. However, such methods would have been very difficult to set up on such a large cohort and over a long period of time. Indeed our aim was to assess patterns of usual behavior, not to make a punctual measurement of physical activity. Second, we considered physical activity level at baseline and we were not able to take into account potential changes in activity level over time, which could influence the patient prognosis (23). Third, patients in this study were recruited in the early 2000s and the outcomes reflect treatment practices in use at the time. At last, the design of the study, which is monocentric and limited to male patients, could constitute a potential restriction to the generalization of the conclusions. However, the consistency of our results with previous studies - which included male and female patients in different countries - led us to assume that our conclusions remain relevant for all CHD patients.

In conclusion, this study - which combines, for the first time, a long term follow up, a complete adjustment on potential confounding factors in CHD and a quantitative assessment of energy expenditure - demonstrates that the level of physical activity in patients presenting with stable CHD is independently associated with long term all-cause mortality.

Conflict of interest

None

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Figure legends

Figure a: Cumulative survival according to physical activity level

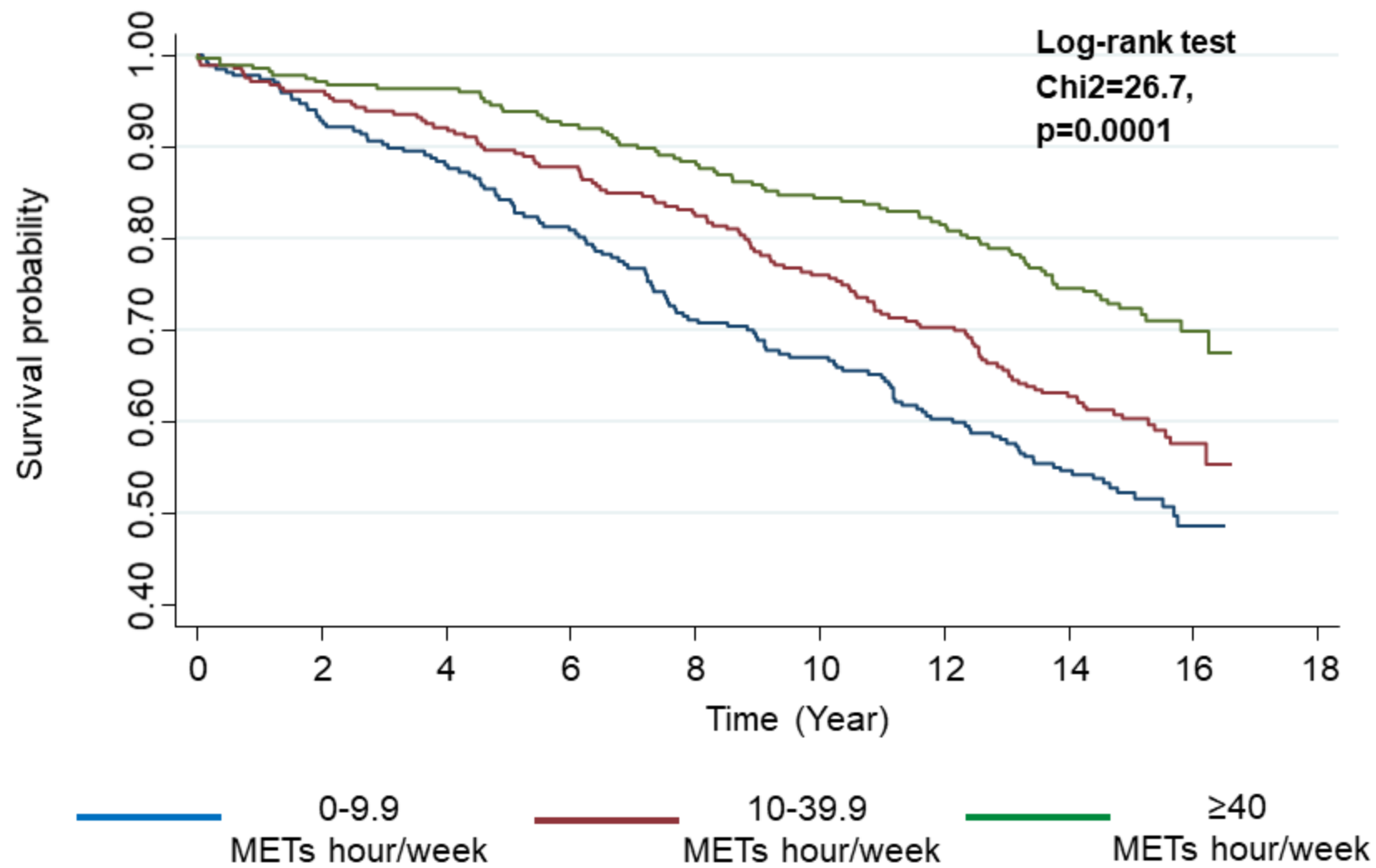
Figure b: Cumulative survival according to physical activity level and level of Left Ventricular Ejection Fraction

Tables

Table 1: Description of the population according to the level of physical activity

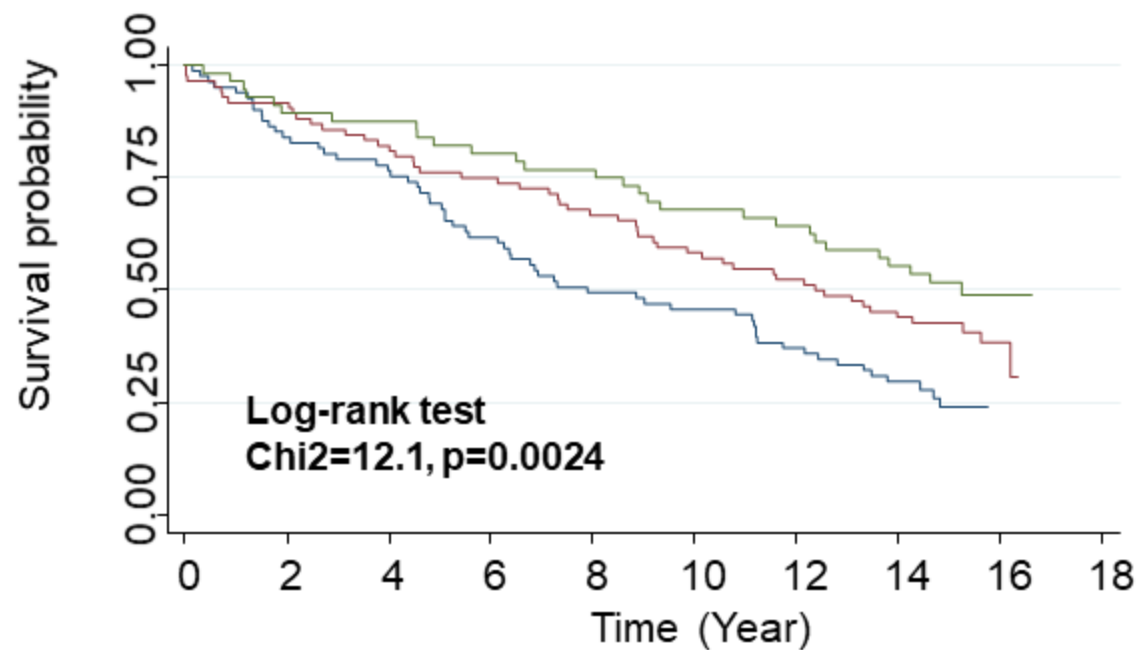
Table 2 : Multivariable Cox regression on the association between levels (tertiles) of physical activity and all-cause death.

Table 3 : Multivariable Cox regression determining independent predictors of all-cause death.



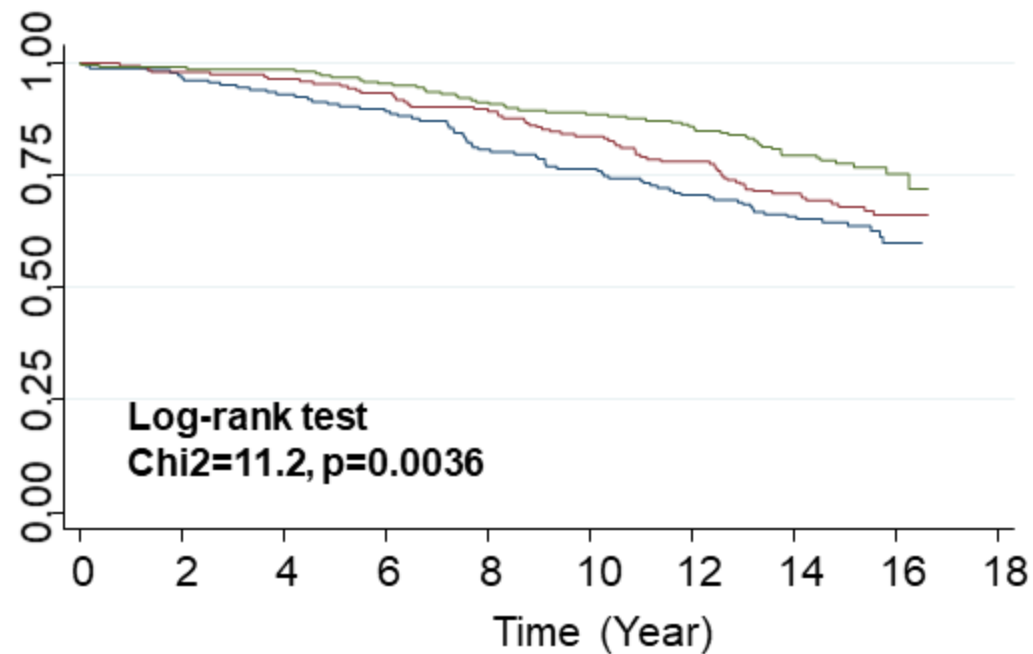
Patients with LVEF < 50%

n=221



Patients with LVEF ≥ 50%

n=601



0-9.9
METs hour/week

10-39.9
METs hour/week

≥40
METs hour/week

Variables	All (n=822)	0-9.9 METs hour per week (n=267)	10-39.9 METs hour per week (n=279)	≥40 METs hour per week (n=276)	p
Age (years)	60.1 (±8.1)	62.9 (±7.5)	61.3 (±7.5)	56.1 (±7.7)	0.001
Waist circumference (cm)	98.9 (±10.9)	100.4 (±11)	100 (±11.2)	96.2 (±10)	0.001
Body mass index (kg/m²)	27.4 (±4.0)	27.6 (±4.1)	27.7 (±4.2)	26.9 (±3.7)	0.037
Heart rate (beat/min)	64.1 (±12.1)	65.2 (±12.5)	64.5 (±12.3)	62.7 (±11.5)	0.05
High Blood Pressure (%)	563 (68.5%)	197 (73.8%)	194 (69.5%)	172 (62.3%)	0.014
Systolic blood pressure (mmHg)	139.5 (±20.6)	141.5 (±20.5)	139 (±20.9)	138.1 (±20.4)	0.15
Diastolic blood pressure (mmHg)	84.6 (±10.7)	84.7 (±10.2)	84.2 (±10.9)	85.1 (±11.0)	0.64
Serum Total Cholesterol (mg/dl)	201 (±44)	199 (±43)	198 (±43)	207 (±44)	0.014
HDLc (mg/dl)	43 (±12)	42 (±12)	43 (±12)	44 (±13)	0.25
LDLc (mg/dl)	125 (±39)	124 (±38)	122 (±38)	130 (±40)	0.06
Triglycerides (mg/dl)	170 (±99)	166 (±91)	167 (±95)	177 (±110)	0.46*
Dyslipidemia	597 (72.7%)	178 (66.9%)	213 (76.6%)	206 (74.9%)	0.026
Diabetes mellitus	243 (29.6%)	84 (31.8%)	90 (32.5%)	69 (25.3%)	0.13
Smoking status					0.011
Non-smoker	143 (17.4%)	50 (18.7%)	49 (17.6%)	44 (15.9%)	

Former smoker	516 (62.8%)	168 (62.9%)	189 (67.7%)	159 (57.6%)	
Current smoker	163 (19.8%)	49 (18.4%)	42 (14.7%)	73 (26.5%)	
hs-CRP (mg/L)	12.9 (\pm 21.9)	15 (\pm 23.7)	13.5 (\pm 25.1)	10.4 (\pm 15.5)	0.015*
Gensini score	46.7 (\pm 40.1)	51.2 (\pm 43.7)	50.1 (\pm 37.6)	38.6 (\pm 37.8)	0.001
Coronary history					<0.001
Previous myocardial infarction	436 (53.2%)	134 (50.2%)	173 (62.0%)	129 (47.1%)	
Previous revascularization in stable context	274 (33.4%)	90 (33.7%)	85 (30.5%)	99 (36.1%)	
CHD treated medically, without revascularization	110 (13.4%)	43 (16.1%)	21 (7.5%)	46 (16.8%)	
Alcohol consumption (g/day)	28.5 (\pm 32.0)	28.7 (\pm 35.7)	28 (\pm 29)	29 (\pm 31.3)	0.65
Duration of disease (months)	42.4 (\pm 65.9)	43.5 (\pm 68.8)	48.9 (\pm 68.6)	34.7 (\pm 59.5)	0.038
Ankle-arm index \leq0.9	274 (33.3%)	102 (38.2%)	101 (36.2%)	71 (25.7%)	0.004
Left Ventricular Ejection Fraction <50%	221 (26.9%)	81 (30.3%)	84 (30.1%)	56 (20.3%)	0.01
Left Ventricular Ejection Fraction (%)	0.53 (\pm 0.14)	0.51 (\pm 0.15)	0.52 (\pm 0.14)	0.55 (\pm 0.12)	0.0068*
Dyslipidemia	525 (63.9%)	161 (60.2%)	191 (68.5%)	173 (62.7%)	0.13
Diabetes	199 (24.2%)	71 (26.6%)	78 (28.0%)	50 (18.1%)	0.014

Hypertension	362 (44.0%)	134 (50.2%)	130 (46.6%)	98 (35.5%)	0.002
Death	324 (39.4%)	130 (48.7%)	115 (41.2%)	79 (26.6%)	<0.0001

Table 1: Description of the population according to the level of physical activity

hs-CRP: high sensitivity C-Reactive Protein; HDL: High Density Lipoprotein; LDL: Low density Lipoprotein

*: analyses performed on log-transformed data

	0-9.9 (n=267)	10-39.9 (n=279)	≥40 (n=276)	p for trend
		HR (95% CI), p	HR (95% CI), p	
Unadjusted	1	0.76 (0.60:0.98), p=0.033	0.48 (0.36:0.63), p=0.001	0.001
Adjusted*	1	0.79 (0.61:1.03), p=0.08	0.71 (0.53:0.96), p=0.025	0.02

Table 2 : Multivariable Cox regression on the association between levels (tertiles) of physical activity and all-cause of death.

*Adjustment for age, dyslipidemia, smoking status, diabetes, high blood pressure, waist circumference, left ventricular ejection fraction, Gensini score, heart rate, ankle-brachial index and duration of disease

Variables	Non-adjusted		Multivariate adjusted	
	HR (95% CI)	p	HR (95% CI)	p
Age (years)	1.05 (1.04;1.07)	0.001	1.04 (1.02;1.06)	0.001
Waist circumference (cm)	1.02 (1.01;1.03)	0.001	1.01 (1.002;1.02)	0.013
Heart rate (beat/mn)	1.02 (1.01;1.03)	0.001	1.01 (1.004;1.02)	0.005
Current smoker	1.34 (0.93;1.94)	0.13	2.21 (1.48;3.31)	0.001
Former smoker	1.33 (0.97;1.82)	0.07	1.37 (0.99;1.89)	0.06
Gensini score	1.37 (1.21;1.56)	0.001	1.12 (0.98;1.29)	0.09
Length of disease (months)	1.05 (1.03;1.07)	0.001	1.03 (1.01;1.05)	0.001
Ankle-arm index ≤ 0.9	1.76 (1.41;2.19)	0.001	1.32 (1.05;1.66)	0.017
Left Ventricular Ejection Fraction <50%	2.83 (2.27;3.52)	0.001	2.17 (1.72;2.75)	0.001
Dyslipidemia	0.69 (0.55;0.86)	0.001	0.70 (0.55;0.88)	0.001
Diabetes mellitus	1.94 (1.54;2.44)	0.001	1.39 (1.08;1.78)	0.009
Hypertension	1.20 (0.96;1.49)	0.10	1.08 (0.86;1.36)	0.50
Physical activity (increase of 10 METs hour per week)	0.91 (0.88;0.94)	0.001	0.95 (0.92;0.98)	0.002

Table 3 : Multivariable Cox regression determining independent predictors of all-cause death