ESC European Society of Cardiology

European Heart Journal (2019) **40**, 1609–1617
doi:10.1093/eurheartj/ehz111

CLINICAL RESEARCH
Prevention and epidemiology

Widespread pain is a risk factor for cardiovascular mortality: results from the Framingham Heart Study

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Received 16 April 2018; revised 4 August 2018; editorial decision 18 January 2019; accepted 20 February 2019; online publish-ahead-of-print 11 March 2019

See page 1618 for the editorial comment on this article (doi: 10.1093/eurheartj/ehz276)

Aims With the introduction of widespread pain (WSP) as a separate diagnostic code in the ICD-11, WSP has now become an own clinical diagnosis independent of the underlying pathophysiology. Research has reported aetiological associations of WSP and cardiovascular diseases. However, studies on mortality risk in individuals with WSP have reported inconsistent results. This study investigates whether there is increased mortality in WSP individuals and establish potential determinants of mortality risk. Therefore, we evaluates the population-based prospective cohort of the Framingham Heart Study (FHS).

Methods and results The FHS is a longitudinal multi-generational study. Pain status was assessed uniquely between 1990 and 1994. Cox proportional hazards modelling was used to estimate hazard ratios (HRs) of WSP on all-cause mortality controlling for sex and age, cardiovascular risk factors, cancer history, lifestyle factors and current medication. WSP examination was carried out in 4746 participants of the FHS (60.3 ± 13.5 years, 55.1% women). A total of 678 (14.5%) subjects fulfilled the criteria for WSP, whereas 4011 (85.5%) subjects did not. The follow-up time was 15 years, during which 202 persons died in the WSP group and 1144 in the no-WSP group. When adjusting for age and sex, all-cause mortality was increased by about 16% in WSP subjects. Individuals with WSP had an increased HR particularly for cardiovascular cause of death (HR adjusted by age and sex = 1.46, 95% confidence interval 1.10–1.94).

Conclusion Our data show that in a large population-based cohort, WSP is associated with increased HR for cardiovascular cause of death, underlining the need for pain assessments in cardiovascular practice.

Keywords Widespread pain • Mortality • Prospective • Population-based • Cohort study

Introduction

Pain conditions of the musculoskeletal system are highly prevalent and associated with a high socioeconomic impact on the individual as well as on society.[1–3] This is especially true for widespread pain (WSP) conditions, which have been related to elevated disability and loss of quality of life.[4,5] Widespread pain specifically presents as a common health problem reported by more than one in ten adults, with prevalence twice as high in women as in men.[6,7] Accordingly, the newly proposed ICD-11 lists WSP as the first diagnosis under the category 'primary pain syndrome', thus setting WSP on the forefront of primary pain conditions.[8]

Though different definitions exist, WSP is usually defined as pain condition with concurrent axial pain and pain of the upper and lower segment, as well as left-sided and right-sided pain.[9,10] Several studies on pain extent have found that the number of painful areas is a strong prognostic factor on its own for the further course of disease.[11–14]

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Despite this relevance, however, there is inconsistent knowledge on the consequences of WSP on physical health and mortality. Previous research has suggested that disabling pain leads to a lifestyle, which is characterized by factors that are likely to be associated with increased mortality risk, such as lower levels of physical activity (PA) and unfavourable nutritional habits leading to obesity and diabetes, sleeping problems, or substance use.[15,16] Interestingly, recent research indicates a possible shared genetic basis between cardiovascular diseases and pain.[17,18] However, the research on this field has only just begun to emerge and thus far, only little is known about the potential consequences of pain on mortality.

Mortality studies, however, are time-consuming and difficult to conduct. Therefore, only few studies have focused on the association of the spatial extent of pain and mortality with inconsistent results.[11,19–25] A recent meta-analysis showed that subjects with WSP experience have higher mortality.[22] Notable, even though there remained an notable risk of cardiovascular death adjusting the risk models for lifestyle variables, the authors concluded that excess mortality is unlikely to be due to the experience of pain *per se* but is explained by lifestyle factors associated with having pain. However, generalizability of these findings was limited due to the high heterogeneity between them and their restriction to European countries. This is aggravated by the fact that all studies to date were limited to official death registers and none of them assessed mortality specific to cardiovascular events and disease in more detail. However, error rates on death certificates are high and extend to ICD-10 coding, thereby affecting most mortality statistics.[26,27] Given this situation, it was unclear until now whether—and if so—how WSP is associated with excess mortality.

Against this background, the primary aim of this study was to investigate whether there is a difference in all-cause mortality between people with and without widespread body pain and to investigate the underlying mechanisms by taking into account socio-demographic characteristics, cardiovascular risk factors, cancer history, and lifestyle factors. For this purpose, we analysed data of the longitudinal multigenerational Framingham Heart Study (FHS) population with a follow-up interval of 15 years and incorporating the detailed review of all medical records and autopsies to minimize the error rates on the official death certificates.[28]

Methods

Study design

This study was carried out as a secondary analysis of data from the population-based Framingham Heart Study (FHS). The FHS is a longitudinal multi-generational study conducted in Framingham, MA, USA.[28] The original cohort started in 1949 and consisted initially of 5209 respondents of a random sample of two-thirds of the adult population characterized by absence of atherosclerotic cardiovascular disease. The 'Framingham Offspring Study' was initiated in 1971 as a sample consisting of the surviving descendants of the original cohort participants and spouses of those descendants. The characteristics and study protocol of both cohorts have been published elsewhere.[28,29] For the present investigation, we included participants of the original cohort and the offspring cohort who were examined between 1990 and 1994 and for whom data of a detailed pain examination were available.

This study complied with the Declaration of Helsinki; written informed consent was obtained from all study participants. The Institutional Review Board of Boston University Medical Center and of Heidelberg University, Medical Faculty Mannheim approved the study protocol (2013-809R-MA).

Pain assessment

Over the study course, pain status was assessed uniquely using a questionnaire in which the spatial extent of pain was determined based on the FHS pain homunculus (Exam 22 in the original cohort, and Exam 5 in the offspring cohort, respectively) for further details, see http://www.framingham heartstudy.org/share/annoated_forms/foapain_2001s_annotated_form.pdf. Therefore, during the exam, all participants were asked whether they had pain, aching or stiffness in any of their joints *on most days*. Persons who answered this question with 'yes' were asked to mark their painful joints on a homunculus with circles showing upper and lower extremity joints, and four areas of the back and neck, and on additional diagrams of both hands (three joints on each finger) and both feet (joints at the base of each toe). Based on the FHS pain homunculus, widespread body pain was classified according to the American College of Rheumatology (ACR) criteria for WSP: this requires axial skeleton pain in addition to pain in two contralateral body quadrants[10] and is further described in FHS-coding manual (see http://www.framinghamheartstudy.org/share/coding_manuals/foapain_2001s_v1_coding_manual.pdf). Additionally, the number of painful areas was assessed according to the number of painful joint areas on the pain homunculus. This count is calculated by summing up the total number of painful joint areas where the participant reported pain. The hands and feet were counted as one site each for this total score (total joint count with a range from 0 to 20 painful areas). See protocol/FHS coding manual for further explanation (http://www.framingham heartstudy.org). The FHS pain homunculus focusses on joint pain without systematic recording of non-joint sites. Accordingly, a clear distinction between pain-free participants and participants with non-joint pain could not be made. Thus, it was not possible to identify a truly pain-free group and we therefore separated the FHS study participants into subjects with WSP vs. those without including subjects with regional pain and no pain.

Outcome

The primary outcome of our study is all-cause mortality with a follow-up time of 15 years after pain assessment. The FHS has clear definitions and monitoring systems for determining day and cause of death for all participants. A panel of three physicians reviewed FHS, medical and hospitalization records and, when available, autopsy reports to assign the underlying cause of death as either: (i) coronary heart disease, (ii) stroke, (iii) other cardiovascular death, (iv) cancer, (v) other causes, or (vi) unknown.[28,30]

Covariates

The influence of potential confounders was analysed by directed acyclic graphs.[31] We used the most recent covariate information during the period of pain assessment (for the original cohort, those variables collected during Exam 22, for the offspring cohort those collected during Exam 5, respectively). Blood samples were taken and level of blood lipids and glucose were measured after a fast of longer than 10 h.[32] Blood pressure was assessed by a physician. Medication (analgesic-narcotics, analgesic-non-narcotics, sleeping pills, antidepressants, and sedatives) were assessed by medical interview, as was smoking status (smoked cigarettes regularly in last year: yes/no) and alcohol consumption (g/day). Physical activity (PA) information was collected using a continuous variable, designed to estimate oxygen consumption. Participants were asked the average number of daily hours (h) spent asleep and at a sedentary, slight, moderate, and heavy PA. The score was calculated as follows: [PA score = $(1.0 \times h_{sleep}) + (1.1 \times h_{sedentary}) + (1.5 \times h_{slight}) + (2.4 \times h_{moderate}) + (5.0 \times h_{heavy})$].[33,34]

Statistical analyses

Descriptive statistics was performed for the total study population and the two subgroups: participants with and without WSP. For continuous variables mean, standard deviation and range were calculated for approximately normally distributed data, otherwise median and range were used. For discrete data, absolute and relative frequencies were computed. Individual survival time after date of pain assessment was computed and right censored after 15 years as prior defined. For survival analysis comparing persons with WSP to those without, Cox proportional hazards modelling was applied and the following covariates were included: crude analysis; Model 1 adjusted for age and sex; Model 2 adjusted for age, sex, and the following cardiovascular risk factors: smoking status, mean arterial blood pressure, body mass index, total blood cholesterol, high-density lipoproteins, blood glucose, medication use (narcotics, non-narcotics, sedative, sleeping pills, antidepressants), alcohol consumption, marital status, and job status; Model 3 adjusted for age, sex, and prior cancer diagnosis. Missing values of covariates were imputed 10 times using chained equations with 100 iterations. For each imputed variable, the set of age, sex, smoking status, mean arterial blood pressure, body mass index, total blood cholesterol, high-density lipoproteins, blood glucose, medication use (narcotics, non-narcotics, sedative, sleeping pills, antidepressants separately), alcohol consumption, marital status, and job status were used as predictor variables. Physical activity was not imputed as descriptive analysis showed systematic missing at an age over 70 years. Initially, a 4th and 5th model was planned using the PA score (4th) and all covariates (5th). However, due to the high number of missing data within this model (1415 subjects with at least one missing covariate, corresponds to 30% of study population) and a systematic missing of PA values in subjects ≥70 years, we decided to abstain from this analysis (see Supplementary material online, Table S1). In addition, association of regions of painful joints (total joint count) with all-cause mortality and cause-specific mortality was analysed using Cox proportional hazards modelling adjusted for age and sex. Proportional hazard assumption was checked for each model. Correlation coefficients between transformed survival time and the scaled Schoenfeld residuals were computed. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated and the group with no WSP was regarded as reference group. The same analysis was carried out for death due to cardiovascular disease, and due to cancer. All *P*-values should be regarded as continuous parameters that reflect the level of evidence and are therefore reported exactly. The data were processed using statistical analysis software (R version 3.1.1 [2014-07-10]). All analyses were performed according to a predefined statistical analysis plan (available on request).

Confounder analyses

Several analyses were performed to examine the influence of potential confounders on the results. The following variables were introduced into the analyses: sex, age, mean arterial blood pressure, body mass index, total blood cholesterol, high-density lipoproteins, blood glucose, cancer history, level of PA, alcohol consumption, smoking status, and use of analgesic medication.

To control for the impact of a present, serious painful disease on the relation between pain and mortality a second analysis was performed. For this purpose, individuals with WSP who died during the first two years after inclusion or exited the study were excluded ($n = 149$).

To examine the impact of drop-outs, non-responder analyses were performed. Non-responder analysis addressed the subjects from whom no pain data were available. In a second step, the drop-out rate was analysed and compared between the two groups (WSP vs. no-WSP).

Results

Subjects

Of the 5022 participants of the FHS (Original and Offspring cohort), 4746 subjects underwent the WSP examination and thus were included in this study. Thereof, 57 subjects were excluded because subjects did not take part in the corresponding examination (thus covariates were not available). Thus, 4689 subjects could be included in the final analyses, with 678 subjects (14.5%) fulfilling the criteria for WSP (WSP group), and 4011 subjects (85.5%) being classified as no-WSP. Follow-up data was missing for 48 subjects, and these subjects were right-censored at the last available contact day (1%, 7 persons in the WSP group, and 41 persons in the no-WSP group).

Descriptive data are presented in *Table 1*. The initial health status was comparable between both groups. The two groups descriptively differed with regard to sex, age, use of analgetic medication, and job status. After adjusting for sex and age, the groups differed in regard to the use of analgetic medication only.

Death events and mortality data

The mean follow-up time was 15.0 years (with 25/75% percentiles: 13/15 years for the overall sample, WSP group, and for the no-WSP group). The absolute number of death events over the follow-up period of 15 years was 1346 (28.4%), with 202 (29.3%) death events in the WSP group compared with 1144 (28.2%) death events in the no-WSP group. Regarding death events with respect to underlying cause, see *Table 2*. The all-cause mortality in the cohort was 22 per 1000 person years, with only slightly increased mortality in individuals initially reporting WSP (22.7/1000 person years compared with 21.9/1000 person years in individuals without WSP).

Based on the hypotheses of this study, mortality was compared between the WSP group and the no-WSP group. When adjusting for age and sex using Cox regression analysis, mortality was higher among individuals with WSP compared with those without (hazard ratio = 1.16, 95% CI 1.00–1.35; $P = 0.051$). *Figure 1* shows the Kaplan–Meier survival curves for all-cause mortality stratified by groups with WSP and without WSP.

When analysing cause of death, report of WSP resulted in an increased HR for cardiovascular (CVD) cause of death (HR adjusted by age and sex = 1.46, 95% CI 1.10–1.94; $P = 0.008$; *Figure 2*), but not for cancer mortality (0.69, 95% CI 0.38–1.27; $P = 0.24$; Supplementary material online, *Figure S1*). Analysing non-fatal events, report of WSP resulted in an increased ratio for CVD events [odds ratio (OR) adjusted by age and sex =1.32, 95% CI 1.07–1.62], but not for cancer events (OR adjusted by age and sex = 0.96, 95% CI 0.74–1.25, see *Table 2*). Additional Cox regression models incorporating the effect of potential confounders showed comparable HRs to the age- and sex-adjusted model (*Table 3*). There was an association between CVD mortality and WSP, while none for cancer mortality. Considering individually the relationship of different medication classes (narcotics, non-narcotics, antidepressants, sedative, and sleeping pills) to overall mortality, for none of these medications a relationship to CVD-related death could be found. Of note, narcotics were related to both overall death (HR = 2.79, 95% CI 1.81–4.31) and cancer-related death (HR = 5.36, 95% CI 2.52–11.4), but not with

Table 1 Sociodemographic characteristics of the study sample of the Framingham Heart Study at baseline pain assessment

	All	No WSP	WSP	*P*-value
Number of subjects	4689	4011	678	
Death events in follow-up of 15 years, *N* (%)	1346 (28.4%)	1144 (28.2%)	202 (29.3%)	0.05
Loss during follow-up	48 (1%)	41 (1%)	7 (1%)	1.00
Follow-up time, median (range)	15.0 (0.02–15.0)	15.0 (0.02–15.0)	15.0 (0.06–15.0)	0.80
Age (years), mean ± SD (range)	60.3 ± 13.5 (26.0–99.0)	60.1 ± 13.7 (26.0–99.0)	61.3±12.1 (31.0–98.0)	0.02
Female sex, *N* (%)	2584 (55.1%)	2129 (53.1%)	455 (67.1%)	<0.001
Total count of painful joints, median, (range)	1.0 (0–20)	1.0 (0–16)	7.0 (3–20)	<0.001
Body mass index (kg/m^2), mean ± SD (range)	27.3 ± 4.9 (14.4–55.6) NA: 117	27.0 ± 4.8 (14.4–55.6) NA: 96	28.7± 5.5 (15.6–49.6) NA: 21	<0.001
Current smoking status, *N* (%)	799 (17.0%) NA: 4	681 (17.0%) NA: 4	118 (17.4%) NA: 0	0.80
Alcohol consumption (g/day), median (range)	1.0 (0.0–42.0) NA: 11	1.0 (0.0–42.0) NA: 11	1.0 (0.0–29.0) NA: 0	<0.001
PA score, median (range)	33.2 (25.9–83.7) NA: 1117	33.2 (25.9–68.6) NA: 995	32.9 (25.9–83.7) NA: 122	0.20
Sitting activities (h), mean ± SD	7.20 ± 2.69	7.17 ± 2.65	7.38 ± 2.91	0.20
Slight PA (h), mean ± SD	6.07 ± 2.28	6.07 ±2.25	6.10 ± 2.40	0.70
Moderate PA (h), mean ± SD	2.69 ± 2.01	2.69 ± 2.00	2.69 ± 2.04	0.80
Severe PA (h), mean ± SD	0 (0–14)	0 (0–10)	0 (0–14)	0.007[a]
Total cholesterol (mg/dL), mean ± SD	203.0 ± 36.8 NA: 129	204.1 ± 36.6 NA: 103	207.7 ± 37.7 NA: 26	0.03
High-density lipoproteins (mg/dL), mean ± SD	49.7 ± 15.3 NA: 144	49.6 ± 15.2 NA: 116	50.2 ± 15.6 NA: 28	0.30
Arterial blood pressure (mmHg), mean ± SD	92.5 ± 3.8 NA: 7	92.3 ± 12.2 NA: 7	93.8 ± 12.0 NA: 0	0.003
Fasting blood glucose (mg/dL), mean ± SD	103.8 ± 33.6 NA: 123	103.5 ± 33.6 NA: 97	105.4 ± 33.5 NA: 26	0.20
Analgetic Medication (any)				
Narcotics	48 (1.0%; NA: 3)	28 (0.7%; NA: 3)	20 (2.9%; NA: 0)	<0.001
Non-narcotics	266 (5.6%; NA: 3)	192 (4.7%; NA: 3)	74 (10.7%; NA: 0)	<0.001
Antidepressants	159 (3.4%; NA: 1)	124 (3.1%; NA: 1)	35 (5.1%; NA: 0)	0.008
Sedativa	140 (3.0%; NA: 2)	103 (2.5%; NA: 1)	37 (5.4%; NA: 0)	<0.001
Sleeping pills	46 (1.0%; NA: 2)	33 (0.81%; NA: 1)	13 (1.7%; NA: 1)	0.01
Merital status				0.20
Single	291 (6.1%)	262 (6.5%)	29 (4.2%)	
Married	3359 (70.8%)	2865 (70.6%)	494 (71.7%)	
Widowed	594 (12.5%)	498 (12.3%)	96 (13.9%)	
Divorced	384 (8.1%)	333 (8.2%)	51 (7.4%)	
Separated	54 (1.1%) NA: 7	46 (1.1%) NA: 7	8 (1.2%) NA: 0	
Job status				<0.001
No occupation	2037 (42.9%)	1686 (41.6%)	351 (50.9%)	
Part-time occupation	2108 (44.4%)	1864 (45.9%)	244 (35.4%)	
Full-time occupation	517 (0.9%) NA: 27	439 (10.9%) NA: 22	78 (11.3%) NA: 5	

Approximately normal-distributed continuous parameters were compared with Student's *t*-test, otherwise with Mann–Whitney *U* test and χ^2 test were used.
NA, not available; PA, physical activity; SD, standard deviation; WSP, widespread pain.
[a]Proportional hazard assumption not fulfilled.

CVD-related death (HR = 1.24, 95% CI 0.38–4.02) in our statistical model.

In the subgroup analyses excluding individuals with WSP who died or exited the study during the first two years after inclusion, the age- and sex-adjusted all-cause mortality among individuals with WSP was HR = 1.16 (95% CI 1.00–1.36, *P* = 0.057), the cardiovascular mortality was HR = 1.47 (95% CI 1.09–1.99, *P* = 0.012), and the cancer mortality was HR = 0.85 (95% CI 0.60–1.20, *P* = 0.35) compared with individuals without WSP. In an additional sensitivity analysis, we repeated all analyses separately for the two cohorts (original cohort and offspring cohort), but they showed the same results (see Supplementary material online, Table S2).

Table 2 Fatal and non-fatal events with respect to underlying cause in subjects with widespread pain compared to those without

Fatal and non-fatal events in the next 15 years	All	No WSP	WSP
Number of subjects, *N* (%)	4689 (100%)	4011 (100%)	678 (100%)
≥1 non-fatal cardiovascular event in follow-up of 15 years, *N* (%)	851 (18.1%)	708 (17.7%)	143 (21.1%)
Death events in follow-up of 15 years, *N* (%)	1346 (28.7%)	1144 (28.2%)	202 (29.3%)
CVD death	344 (7.3%)	285 (7.0%)	59 (8.6%)
CHD death	136 (2.9%)	113 (2.8%)	23 (3.3%)
CVA death	91 (1.9%)	77 (1.9%)	14 (2.0%)
Other CVD death	117 (2.5%)	95 (2.3%)	22 (3.2%)
Cancer death	342 (7.3%)	302 (7.4%)	40 (5.8%)
Subjects with cancer in follow-up of 15 years, *N* (%)	1315(28.4%)	1136(28.3)	179(26.4)
Other reasons	546 (11.6%)	467 (11.5%)	79 (11.5%)
Cause unknown	114 (2.4%)	90 (2.2%)	24 (3.5%)
Loss to follow-up	48 (1.0%)	41 (1.0%)	7 (1.0%)

CHD, coronary heart disease; CVA, cerebral vascular accident (stroke); CVD, cardiovascular disease; WSP, widespread pain.

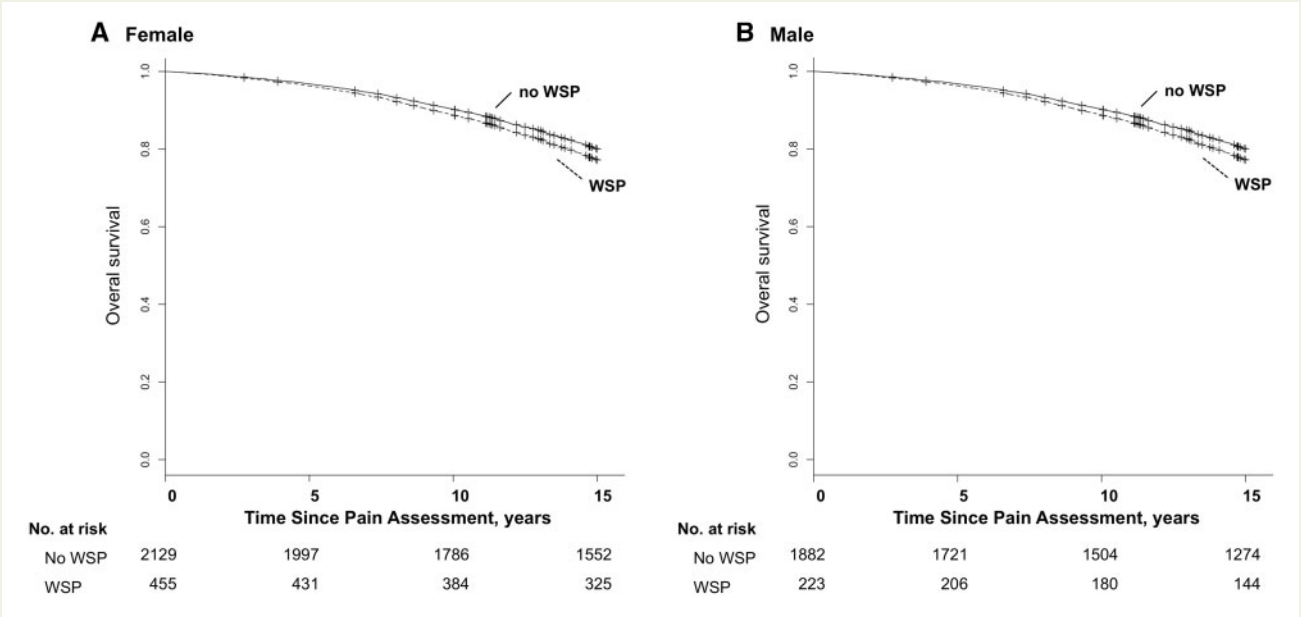


Figure 1 Overall survival rates in widespread pain. Survival related to initial pain assessment in females (*A*) and males (*B*). Survival curves adjusted for age during the observation period (15 years) stratified by groups with no widespread pain report (no-WSP, upper curve) and with widespread pain (WSP, lower curve). For both endpoints, the curves diverge continuously and significantly throughout the 15 years of follow-up. Crosses indicate censored cases.

The number of painful regions (total joint count) was significantly linked to all-cause mortality. Cox regression modelling with adjustment for age and sex showed higher mortality in subjects with more pain regions: HR = 1.03 per painful region (95% CI 1.01–1.04; $P < 0.004$). Similar to WSP, the number of painful regions was associated with cardiovascular mortality (HR = 1.05, 95% CI 1.02–1.08; $P < 0.004$) but not with cancer mortality (HR = 0.99, 95% CI 0.96–1.03; $P = 0.65$).

Non-responder analyses

A first non-responder analysis addressed the subjects from whom no pain data were available. Out of these 276 (5%) subjects, 184 were female (67%), and these persons were in average 10 years older than the subjects with pain data. Other systemic cardiovascular parameters were comparable. In the study follow-up period of 15 years, 48 subjects (1%) dropped out of the study [41 in the no-WSP group (1.0%), and 7 in the WSP group (1.0%)].

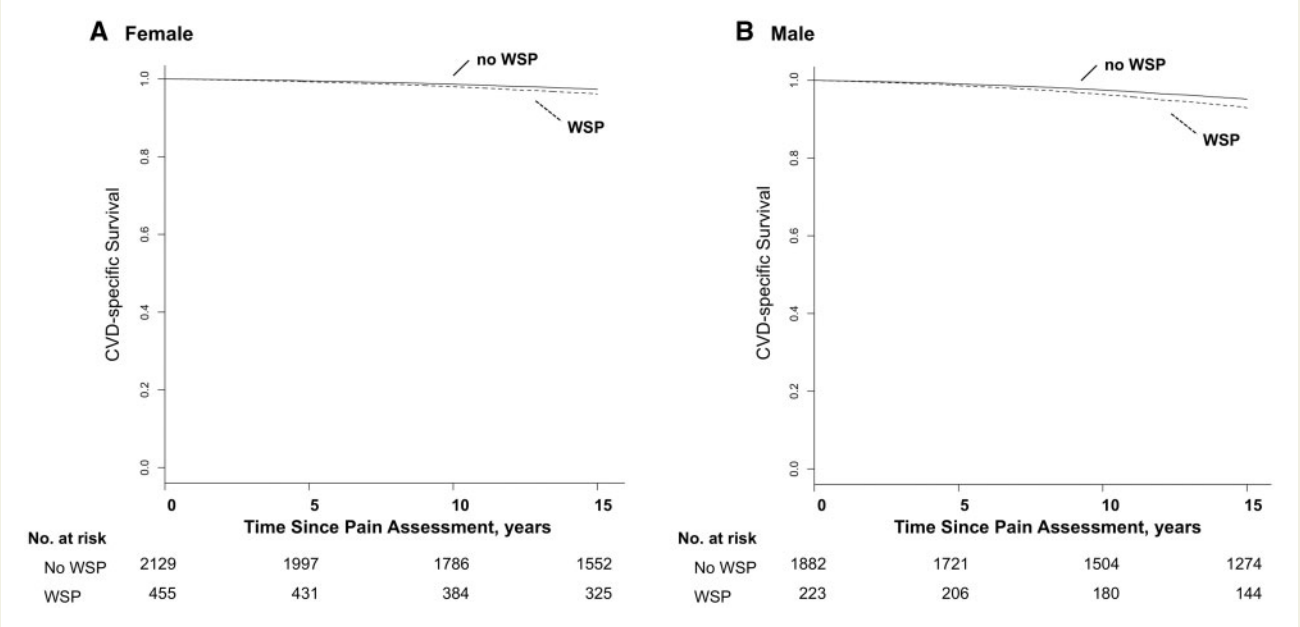


Figure 2 CVD mortality related to initial pain assessment. CVD mortality related to initial pain assessment in females (*A*) and males (*B*). Survival curves adjusted for age during the observation period (15 years) stratified by groups with no widespread pain report (no-WSP, upper curve) and with widespread pain (WSP, lower curve). For both endpoints, the curves diverge continuously and significantly throughout the 15 years of follow-up. Marking of censored subjects was abandoned for better illustration of the curves due to the high number of censored cases with death due to cancer reasons.

Table 3 Mortality in relation to report of widespread pain vs. not, and confounding factors

	Crude	Model 1			Model 2			Model 3		
	All-cause mortality	All-cause mortality	CVD mortality	Cancer mortality	All-cause mortality	CVD mortality	Cancer mortality	All-cause mortality	CVD mortality	Cancer mortality
No WSP	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
WSP	1.04[a]	1.16	1.46	0.69	1.06	1.38	0.76	1.16	1.46	0.74
	(0.89–1.21)	(1.00–1.35)	(1.10–1.94)	(0.38–1.27)	(0.91–1.24)	(1.03–1.84)	(0.54–1.07)	(1.00–1.35)	(1.10–1.94)	(0.40–1.35)
P-value	0.62	0.051	0.008	0.235	0.45	0.033	0.115	0.050	0.008	0.322
n/events/ missings[b]	4689/1346/0	4689/1346/0	4689/344/0	4689/342/0	4689/1346/0	4689/1346/0	4689/1346/0	4689/1346/0	4689/344/0	4689/342/0

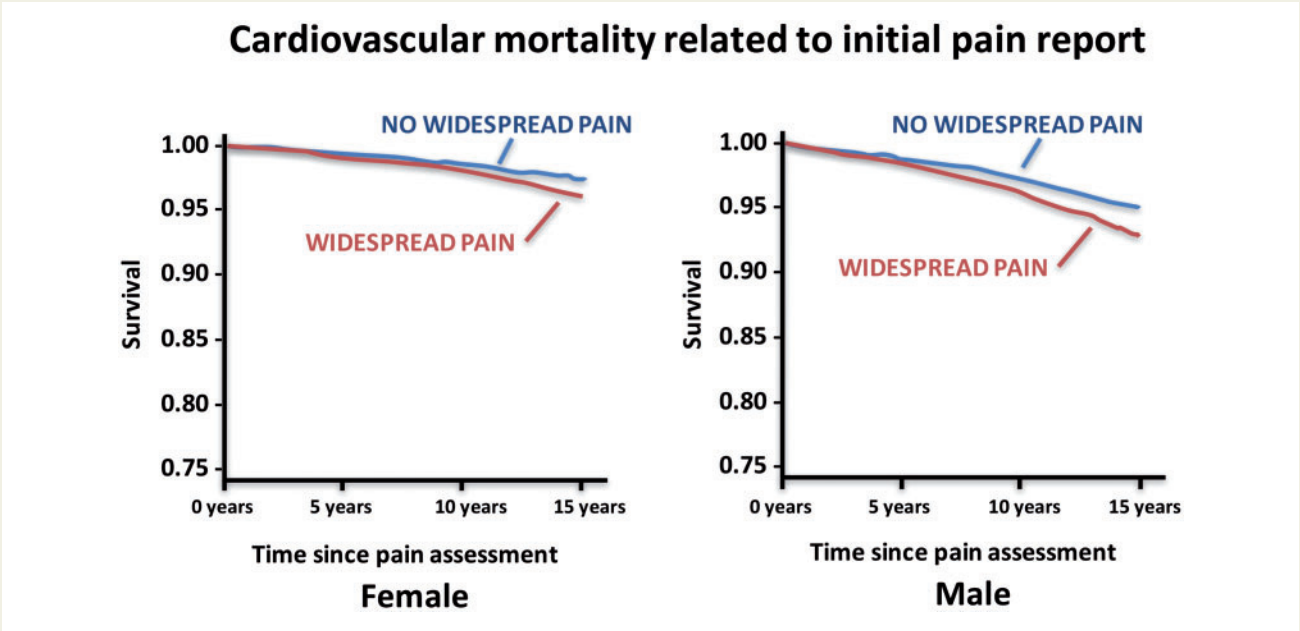
Crude and adjusted hazard ratios with 95% confidence intervals.
CVD, cardiovascular disease; WSP, widespread pain.
[a]Proportional hazard assumption not fulfilled.
[b]*n*/events/observations deleted due to missings.
- Model 1 is adjusted for sex and age.
- Model 2 ('cardiovascular') is additionally adjusted for cardiovascular risk factors: smoking status, mean arterial blood pressure, body mass index, total blood cholesterol, high density lipoproteins, blood glucose, medication use (narcotics, non-narcotics, sedative, sleeping pills, antidepressants), alcohol consumption, marital status, and job status.
- Model 3 ('cancer') is adjusted for sex, age and cancer history.

Discussion

The primary aim of this study was to explore whether there is a difference in all-cause mortality between people who report WSP and those who do not. The current study found that all-cause mortality was increased by about 16% in WSP subjects, largely accounted for by cardiovascular events, but not for cancer mortality.

Cardiovascular mortality

Our results provide evidence that WSP was associated specifically with increased risk for cardiovascular cause of death, but not for cancer mortality. Focusing on cardiovascular events, cox proportional hazards modelling revealed an increase in cardiovascular causes of death of more than 40% in the WSP group compared with the no-



Take home figure Cardiovascular mortality related to initial pain assessment in females and males. Survival curves adjusted for age during the observation period stratified by groups with no widespread pain (upper curve) and with widespread pain (lower curve). For both endpoints, the curves diverge continuously and significantly throughout the 15 years of follow-up.

WSP group. The association between WSP and an excess in cardiovascular mortality is in line with a recent meta-analysis including data from the UK Biobank that found an increased mortality risk due to cardiovascular disease in individuals with WSP.[22] Notable, even though there remained an notable risk of cardiovascular death adjusting the risk models for lifestyle variables in this study, the authors concluded that excess mortality unlikely to be due to the experience of pain *per se* but is explained by lifestyle factors associated with having pain.[22] But this conclusion is not supported by the findings presented here where additional analyses incorporating the effect of lifestyle factors showed comparable HRs to the age- and sex-adjusted model. Considering lifestyle factors this study focused on PA and substance use (smoking, alcohol, and medication) as potential predictors of mortality. However, indicators of PA level and its associated subcategories (time spent in sitting activities, slight physical activities, moderate physical activities, or heavy physical activities), smoking status as well as substance use were similar between the WSP and no-WSP group indicating that these variables do not play a pivotal role. In particular, the small differences in the activity measures were a little surprising, but might be explained by the generally very low level of activity in this FHS study cohort. Of note, various analgesic medications have been related to cardiovascular mortality. However, in our analyses, none of the medication classes assessed in this cohort were related to CVD-related death. Although there was a relationship between narcotics and both overall mortality and cancer-related mortality, there was no relationship of narcotics to CVD-related mortality. Interestingly, a Swedish study suggested that psychosocial factors such as level of perceived stress and sleeping problems might be of particular importance in this respect.[35] In line with this, a recent editorial highlights in particular the importance of also attending to the psychosocial domains of WSP and their multifaceted potential consequences, including the mediation between WSP and increased mortality.[36] Further studies regarding the association between psychosocial stress, WSP and mortality would be needed to establish the role of these variables with more confidence.

Cancer mortality

Earlier studies reported an association between the report of WSP and subsequent death from cancer in the medium and long term.[22] However, the mortality data from the population-based cohort of the FHS presented here do not support this previous research. In contrast to earlier findings, when analysing cause of death, cancer mortality did not differ significantly between the WSP and no-WSP group, this result was still present when adjusting for a previous history of cancer. This finding might be related to the strength of the FHS focusing specifically on phenotyping cardiovascular events. Feasibly, lethal cardiovascular events caused by or in the context of cancer may more likely be identified as CVD death than in other studies, in which any death in the course of cancer is often classified as death by cancer. Speculatively, cancer patients with comorbid WSP may be at an increased risk to die from cardiovascular events than cancer patients without comorbid WSP.

Strengths and limitations

Some limitations of this study have to be mentioned including that pain assessment and definition differed from previous studies. Assessment of joint pain in the FHS did neither address temporal aspects of pain in more detail, nor the severity or the underlying pathophysiology of the pain. Even though the FHS pain assessment asked for pain *on most days,* temporal aspects of pain were not explicitly quantified. Similar, severity of pain was not assessed. Hence, no

distinction between acute and chronic pain could be made, and it was not possible to evaluate the pain-related immobility. However, a previous study found that increased mortality for individuals with WSP was independent of pain duration and that there is no difference in mortality between individuals with regional chronic pain and individuals without chronic pain.[35] Further, FHS pain homunculus represents primarily a joint pain assessment, which did not specifically consider pain at non-joint sites. Pain at non-joint sites could not be ruled out with certainty. Consequently, it was not possible to define a 'regional pain' or truly 'pain-free' group. Furthermore, it was not possible to take into account the pathophysiological processes underlying the pain. In this respect, more detailed information on 'specific' reasons of pain (degeneration, rheumatic disease, post-trauma, etc.) would have been desirable. Initially, analyses on the presence of rheumatoid arthritis were planned. However, the data regarding the presence of rheumatoid arthritis were incomplete (only in the original cohort), and the overall prevalence of rheumatic arthritis patients in this subgroup was not very high (49/993). A sensitivity analysis after exclusion of these subjects showed no relevant impact on the results in this subgroup.

Another limitation of this study is the missing consideration of psychosocial factors such as the individual level of distress and pain related disability, but also socio-economic variables such as income and educational attainment have not been taken into account.

Among the strengths of our study stand the large population-based cohort design, the long observation period with regular exams, the detailed documentation of causes leading to death including autopsies, the careful ascertainment of cardiovascular risk factors based on blood samples and clinical evaluation. Notably, this study is, to our knowledge, the first to assess mortality associated with WSP incorporating a detailed review of medical records and autopsies to minimize the error rates on the official death certificates, as well as detailed documentation of causes leading to death including the careful ascertainment of cardiovascular risk factors based on blood samples and clinical evaluation. Moreover, clinical outcomes were ascertained using detailed review of all medical records. With this approach we can show that the risk of cardiovascular mortality associated with WSP has so far been underestimated. This could have implications for clinical practice in the future. Although clinical guidelines do mention the importance of mental stressors and explicitly recommend the evaluation of psychosocial risk factors in clinical practice,[37] the evaluation of chronic and generalized pain has so far not been included. And this despite the fact that chronic pain is by far the most common global cause of health impairment and probably one of the most common stressors at all.

Conclusions

Taken together, the findings of this research demonstrate that all-cause mortality is increased in individuals with WSP. It is shown that WSP is associated with increased risk for cardiovascular death, but not for cancer mortality. This increased risk is independent from age and gender, PA, medication use as well as multiple cardiovascular risk factors. It is upon future research to show whether and which psychosocial factors may explain the excess mortality seen in WSP subjects.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

This work was supported by the SFB1158 of the Deutsche Forschungsgemeinschaft. This work was also supported by the German Federal Ministry of Education and Research (LOGIN consortium, FKZ: 01EC1010A and 01EC1010B to W.E.).

Conflict of interest: none declared.

References

1. Krismer M, van Tulder M. Strategies for prevention and management of musculoskeletal conditions. Low back pain (non-specific). *Best Pract Res Clin Rheumatol* 2007;**21**:77–91.
2. Maetzel A, Li L. The economic burden of low back pain: a review of studies published between 1996 and 2001. *Best Pract Res Clin Rheumatol* 2002;**16**:23–30.
3. Pincus T, Burton AK, Vogel S, Field AP. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. *Spine* 2002;**27**:E109–E120.
4. Tesarz J, Gerhardt A, Hartmann M, Kohlmann T, Eich W. The course of the spatial extent of pain in non-specific chronic back pain: a prospective population-based cohort study with clinical evaluation. *Clin J Pain* 2016;**32**:580–587.
5. Häuser W, Schmutzer G, Glaesmer H, Brähler E. Prävalenz und Prädiktoren von Schmerzen in mehreren Körperregionen. *Schmerz* 2009;**23**:461–470.
6. Gerhardt A, Hartmann M, Blumenstiel K, Tesarz J, Eich W. The prevalence rate and the role of the spatial extent of the pain in chronic back pain—a population-based study. *Pain Med* 2014;**15**:1200–1210.
7. Gran JT. The epidemiology of chronic generalized musculoskeletal pain. *Best Pract Res Clin Rheumatol* 2003;**17**:547–561.
8. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JW, Wang SJ. A classification of chronic pain for ICD-11. *Pain* 2015;**156**:1003–1007.
9. Harkness EF, Macfarlane GJ, Silman AJ, McBeth J. Is musculoskeletal pain more common now than 40 years ago?: two population-based cross-sectional studies. *Rheumatology* 2005;**44**:890–895.
10. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis Rheum* 1990;**33**:160–172.
11. Andersson HI. The course of non-malignant chronic pain: a 12-year follow-up of a cohort from the general population. *Eur J Pain* 2004;**8**:47–53.
12. Bergman S, Herrström P, Jacobsson LT, Petersson IF. Chronic widespread pain: a three year followup of pain distribution and risk factors. *J Rheumatol* 2002;**29**:818–825.
13. Larsson B, Björk J, Börsbo B, Gerdle B. A systematic review of risk factors associated with transitioning from regional musculoskeletal pain to chronic widespread pain. *Eur J Pain* 2012;**16**:1084–1093.
14. Staud R. Predictors of clinical pain intensity in patients with fibromyalgia syndrome. *Curr Rheumatol Rep* 2004;**6**:281–286.
15. Vandenkerkhof E, MacDonald H, Jones G, Power C, Macfarlane G. Diet, lifestyle and chronic widespread pain: results from the 1958 British Birth Cohort Study. *Pain Res Manag* 2011;**16**:87–92.
16. Fayaz A, Ayis S, Panesar S, Langford R, Donaldson L. Assessing the relationship between chronic pain and cardiovascular disease: a systematic review and meta-analysis. *Scand J Pain* 2016;**13**:76–90.
17. Winsvold B, Bettella F, Witoelar A, Anttila V, Gormley P, Kurth T, Terwindt G, Freilinger T, Frei O, Shadrin A, Wang Y, Dale A, van den Maagdenberg A, Chasman D, Nyholt D, Palotie A, Andreassen O, Zwart J, Consortium IHG. Shared genetic risk between migraine and coronary artery disease: a genome-wide analysis of common variants. *PLoS One* 2017;**12**:e0185663.
18. van Hecke O, Hocking L, Torrance N, Campbell A, Padmanabhan S, Porteous D, McIntosh A, Burri A, Tanaka H, Williams F, Smith B. Chronic pain, depression and cardiovascular disease linked through a shared genetic predisposition: analysis of a family-based cohort and twin study. *PLoS One* 2017;**12**:e0170653.
19. McBeth J, Symmons DP, Silman AJ, Allison T, Webb R, Brammah T, Macfarlane GJ. Musculoskeletal pain is associated with a long-term increased risk of cancer and cardiovascular-related mortality. *Rheumatology* 2008;**48**:74–77.

20. Macfarlane G, Jones G, Knekt P, Aromaa A, McBeth J, Mikkelsson M, Heliovaara M. Is the report of widespread body pain associated with long-term increased mortality? Data from the Mini-Finland Health Survey. *Rheumatology* 2007;**46**: 805–807.
21. Macfarlane G, McBeth J, Silman A. Widespread body pain and mortality: prospective population based study. *BMJ* 2001;**323**:662–665.
22. Macfarlane G, Barnish M, Jones G. Persons with chronic widespread pain experience excess mortality: longitudinal results from UK Biobank and meta-analysis. *Ann Rheum Dis* 2017;**76**:1815–1822.
23. Úsberg A, Stovner L, Zwart J, Winsvold B, Heuch I, Hagen K. Chronic musculoskeletal complaints as a predictor of mortality-The HUNT study. *Pain* 2016;**157**: 1443–1447.
24. Andorsen O, Ahmed L, Emaus N, Klouman E. Musculoskeletal complaints (pain and/or stiffness) and their impact on mortality in the general population. The Tromsø Study. *PLoS One* 2016;**11**:e0164341.
25. Úsberg A, Heuch I, Hagen K. The mortality associated with chronic widespread musculoskeletal complaints: a systematic review of the literature. *Musculoskeletal Care* 2017;**15**:104–113.
26. McGivern L, Shulman L, Carney J, Shapiro S, Bundock E. Death certification errors and the effect on mortality statistics. *Public Health Rep* 2017;**132**:669–675.
27. Weinstock M, Bogaars H, Ashley M, Litle V, Bilodeau E, Kimmel S. Inaccuracies in certification of nonmelanoma skin cancer deaths. *Am J Public Health* 1992;**82**: 278–281.
28. Dawber T, Meadors G, Moore F. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health Nations Health* 1951;**41**:279–281.
29. Kannel W, Feinleib M, McNamara P, Garrison R, Castelli W. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol* 1979;**110**:281–290.
30. Lloyd-Jones D, Martin D, Larson M, Levy D. Accuracy of death certificates for coding coronary heart disease as the cause of death. *Ann Intern Med* 1998;**129**: 1020–1026.
31. Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology* 2011;**22**:745.
32. Elias M, Sullivan L, D'Agostino R, Elias P, Jacques P, Selhub J, Seshadri S, Au R, Beiser A, Wolf P. Homocysteine and cognitive performance in the Framingham offspring study: age is important. *Am J Epidemiol* 2005;**162**:644–653.
33. Kannel W, Sorlie P. Some health benefits of physical activity. The Framingham Study. *Arch Intern Med* 1979;**139**:857–866.
34. Shortreed S, Peeters A, Forbes A. Estimating the effect of long-term physical activity on cardiovascular disease and mortality: evidence from the Framingham Heart Study. *Heart* 2013;**99**:649–654.
35. Andersson H. Increased mortality among individuals with chronic widespread pain relates to lifestyle factors: a prospective population-based study. *Disabil Rehabil* 2009;**31**:1980–1987.
36. Da Silva J, Geenen R, Jacobs J. Chronic widespread pain and increased mortality: biopsychosocial interconnections. *Ann Rheum Dis* 2018;**77**:790–792.
37. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.