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Cardiovascular Disease Risk Factors Predict the Development and Numbers of Common Musculoskeletal Disorders in a Prospective Cohort

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Objective: The aim of the study is to assess risk of common musculoskeletal disorders (MSDs) based on cardiovascular disease (CVD) risk scores. **Methods:** Data from a 9-year prospective cohort of 1224 workers in three states were analyzed. Baseline data included questionnaires, structured interviews, physical examinations, anthropometric measurements, nerve conduction studies, and individualized measurement of job physical factors. Monthly follow-ups were conducted. Framingham risk scores were calculated. A priori case definitions were constructed for carpal tunnel syndrome, lateral epicondylopathy, medial epicondylopathy, and rotator cuff tendinopathy. **Results:** Adjusted RRs for one or more MSDs increased to 3.90 (95% confidence interval, 2.20–6.90) among those with 10-year cardiovascular disease risk scores greater than 15% and 17.4 (95% confidence interval, 3.85–78.62) among those with more than 4 disorders. **Conclusions:** Cardiovascular disease factors are strongly associated with the subsequent development of common MSDs. Risks among those with multiple MSDs are considerably stronger.

Key Words: cardiovascular disease, epidemiology, prospective cohort, epicondylitis, supraspinatus, vascular, blood flow

LEARNING OUTCOMES

- Define the study design type and identify where that study design type ranks on the pyramid of evidence.
- Quantify the upper limit for relative risk for someone with one musculoskeletal disorder and high cardiovascular risks.
- Quantify the upper limit for relative risk for someone with four or more musculoskeletal disorders and high cardiovascular risks.

Musculoskeletal disorders (MSDs), including carpal tunnel syndrome (CTS), lateral epicondylopathy, and rotator cuff tendinopathy, have high prevalence rates. Carpal tunnel syndrome is the most common peripheral entrapment neuropathy, with prevalence estimates of 1% to 5% among the general population.[1–3] Among workers whose tasks require combinations of forceful and repetitive movements, that prevalence estimate rises to 5% to 21%.[4,5] This trend of increased risk is borne out in annual incidence estimates for CTS, which for the general population is 1 to 3 cases per 1000 person years and up to 14.8 per 1000 person years in various occupational cohorts.[6] An even wider range of prevalence is seen in cases of lateral epicondylopathy, which has been estimated to range from 0.2% to 41.2%.[7–23] A systematic review of 4629 postmortem examinations reported an overall prevalence of complete rotator cuff tears of 23%[24]; however, the prevalence of rotator cuff tendinopathy and tears on magnetic resonance imaging increases with age and is more than 50% by ages 55 to 60 years.[25,26]

The rates of these disorders lead to substantial costs, with annual costs of CTS estimated at $2 billion (US), with a majority of this cost stemming from the 450,000 surgical releases conducted annually and the accompanying lost work time.[27] Significant indirect costs have also been associated with CTS, regardless of surgery, with a lifetime cost estimate of $30,000 per case.[3,28,29] Costs of rotator cuff repairs have been estimated at $6904 to $12,979 per case.[30,31] The aggregate cost of upper extremity MSDs are thus estimated at $6.5 to $6.8 billion.[32,33]

An increasing body of evidence has indicated the importance of systemic risk factors in developing musculoskeletal disorders. There is accumulating evidence that diabetes mellitus,[34–39] metabolic syndrome,[40–42] insulin resistance,[43] carotid intima-media thickness,[44–46] low-density lipoprotein cholesterol,[47] obesity,[12,48–53] waist circumference,[54,55] and lack of vigorous exercise[56] have roles in the development of CTS. Forceful use combined with repetition has also been shown to increase risk in the occupational setting.[49,57–60]

Evidence of risk factors for lateral epicondylopathy is quite sparse because there have been few prospective cohort studies. Reported risks from longitudinal studies include age,[8,61–65] obesity,[62] low social support,[62,66] and depression.[65] As with CTS, combinations of force and repetition have also been shown to be occupational risk factors.[63,67,68] Finally, risk factors for rotator cuff tendinopathy include obesity,[69–71] smoking,[72–76] hypercholesterolemia,[77] and diabetes mellitus.[78–80] Job risks are poorly defined for this disorder but are thought to include force, posture, and repetition.[81–83] Having greater numbers of cardiovascular disease (CVD) risk factors has been associated with both increased risk of, and severity of, rotator cuff tears.[84] Cardiovascular risk factors have also been shown to result in worse function and poorer healing of surgically repaired rotator cuff tendons.[85–88]

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Previous analyses of data from this study were conducted to test for an association between CVD risk and the development of CTS,[89] lateral epicondylopathy,[90] and rotator cuff tendinopathy.[91] Those cross-sectional baseline analyses reported increased associated risks based on associative rather than prospective data.

The purpose of this study is to report whether the Framingham Heart Study-based CVD risk scores at baseline predict the subsequent development of four common MSDs. If CVD risk factors predict the development of MSDs, then a new avenue of prevention may be possible, which would require subsequent exploration.

METHODS

Institutional review boards of the University of Utah, University of Wisconsin-Milwaukee, and Medical College of Wisconsin approved this study. Data collection instruments and methods have been previously reported.[92]

Participants were recruited from 17 facilities in the states of Illinois, Utah, and Wisconsin. These employment sectors included manufacturing, healthcare, office jobs, and food processing. Within each of these industries, participants were employed in various jobs. Participants provided informed consent and were enrolled irrespective of whether they had any symptoms or disorders.

This research was conducted by two teams of researchers that were blinded to each other: the Health Outcomes Assessment Teams (hereafter referred to as the "Health Team") and the Job Physical Assessment Teams (hereafter referred to as the "Job Team").

The Health Team administered assessments to all workers regardless of the presence or absence of symptoms of both musculoskeletal disorders and CVD. These assessments consisted of questionnaires, structured interviews, two standardized physical examinations, and nerve conduction studies (NCSs).

Questionnaires included demographic variables, medical conditions (eg, diabetes mellitus, tobacco use), hobbies, exercise habits, and psychosocial factors (eg, depression, job satisfaction). Structured interviews inquired about symptoms localized according to a structured symptoms diagram.[92] For CTS, the localized symptoms were tingling and numbness. For lateral and medial epicondylopathy, symptoms localized to the lateral and medial epicondyle were required. For rotator cuff tendinopathy, glenohumeral joint pain was required. Blood pressure was measured, as were height and weight. The latter measurements were used to calculate body mass indices (BMIs). Physical examinations were standardized and included palpation and provocative maneuvers.

Nerve conduction studies were performed on each hand regardless of the presence or absence of baseline symptoms. Examiners from the Health Team who performed NCSs were blinded to the worker's symptoms and job physical requirements. Nerve conduction studies were conducted in accordance with the guidelines of the American Association of Neuromuscular and Electrodiagnostic Medicine.[93] The participants' hands were warmed as necessary, to achieve a minimum hand temperature of 30°C. Antidromic sensory, motor, and transcarpal measures were assessed at 14 cm for sensory, 8 cm for motor, and 8 cm for transcarpal measures. The transcarpal delta is the difference between a person's sensory latencies for the median and ulnar nerves in the same hand. The cutpoints for determining abnormal findings were 3.7 ms or less for sensory latency; 4.5 ms or less for motor latency; and 0.55 ms or less for transcarpal measures. Persons with abnormal findings in both median and ulnar nerves were excluded as those findings were determined to be potentially consistent with polyneuropathy. Those with a peak ulnar latency of at least 3.68 ms were also classified as potential polyneuropathy and were thus excluded. Those with transcarpal delta greater than 0.55 ms were classified as abnormal and consistent with median mononeuropathy.

Study subjects were followed monthly for the development of symptoms of MSDs. Symptoms of potential CTS required paresthesias (tingling and/or numbness) in at least two of the first four radial digits (thumb, index, middle, and/or ring finger). The case definition of CTS required both: (1) paresthesias for at least seven continuous days or three recurrences of paresthesias in the past 12 months and (2) an abnormal NCS consistent with CTS.

Lateral epicondylopathy required lateral epicondylar pain plus tenderness on palpation at one of six lateral epicondylar tender points.[94] Medial epicondylopathy required medial epicondylar pain plus tenderness on palpation at one of two medial epicondylar tender points. Rotator cuff tendinopathy required glenohumeral shoulder pain plus at least one provocative maneuver (painful arc, supraspinatus testing, and/or Neer impingement).

The procedures used for monthly follow-ups were the same as those that were performed at the baseline assessment. Nerve conduction studies were performed every 6 months for those who had reported any paresthesias in the prior 6-month interval.

Physical exposures from the worker's job tasks were quantified by the Job Team. This included analyses of videotapes and measurements to quantify hand/wrist exposures as assessed by the Strain Index. The Strain Index includes six individually rated measures, which are multiplied to calculate the Strain Index (force, rate of repetition, duration of exertion, hand/wrist posture, speed of the work, and duration of the tasks per day).[57,92,95]

Cardiovascular disease risk factors were assigned a point value that was stratified by sex, according to the Framingham Heart Study model.[96] These variables included age, tobacco use, diabetes, and hypertension that was either treated and untreated, measured, or self-reported. As cholesterol was not measured, it was not included in the scores. Body mass index is not incorporated in the original Framingham score but was included in the adjusted analyses herein. Each person had a CVD risk score calculated by summing the point values of individual variables in accordance with the Framingham Study.[97]

As Framingham CVD risk scores range from 0 to 29, there would naturally be insufficient incident cases to analyze risk by each of 30 categories in a working age population of 1,203. Therefore, an a priori decision was made to collapse the categories into six categories of the population. These collapsed six categories consisted of 10-year risk scores of 0 to 2, 3 to 5, 6 to 8, 9 to 11, 12 to 14, and 15% or more. This collapsing was done without knowledge of the MSDs case distribution.

Statistical Analyses

Analyses were performed at the level of a person. Descriptive data were analyzed. The numbers of musculoskeletal disorder events meeting the case definitions were tallied. Framingham risk scores were calculated. Logistic regression analyses were performed. Data were next adjusted with the following factors in the model: BMI, measured Strain Indices, job satisfaction, and feelings of depression. These factors were selected based on prior evaluation and identification as potential risk factors.[63,91,92] The data were analyzed separately for prevalent baseline cases and incident cases in the course of the cohort follow-up. Because there were not meaningfully different results for the prevalent and incident cases, the combined analyses are presented to provide more stable risk estimates.

RESULTS

The study enrolled 1224 participants, of which 1203 had complete data and were included in analyses. The mean age was 42.2 ± 11.4 years (Table 1). The population was 66.0% female and 34.0% male. The mean blood pressures were 127.6 ± 17.6 mm Hg systolic and 79.7 ± 10.8 mm Hg diastolic. A plurality (47.9%) were never smokers, while 27.7% currently smoked. Considerable proportions reported having hypertension (n = 200, 16.6%) and high cholesterol (n = 213, 17.7%). Smaller proportions reported a history of diabetes

TABLE 1. Descriptive Data on the Study Cohort (*N* = 1,203).

Category	*n* (%)	Mean (SD)
Age	1,203	42.2 (11.4)
BMI (kg/m^2)	1,203	29.5 (6.8)
Strain Index (typical job tasks)	1,074	8.7 (10.4)
Framingham Risk Scores	1,203	6.4 (5.1)
Diastolic blood pressure (mm Hg)	1,199	79.7 (10.8)
Systolic blood pressure (mm Hg)	1,203	127.6 (17.1)
Sex		
Female	794 (66.0)	
Tobacco use		
Never	576 (47.9)	
Yes, smoked in past	294 (24.4)	
Yes, current smoker	333 (27.7)	
High blood pressure history	200 (16.6)	
High cholesterol history	213 (17.7)	
Education		
College graduate (bachelor's degree or higher)	44 (3.7)	
Some college	331 (27.5)	
High school graduate or GED	665 (55.3)	
Some high school	104 (8.7)	
8th-grade or less	33 (2.7)	
Diabetes mellitus	64 (5.3)	
Felt depressed		
Always	23 (1.9)	
Often	206 (17.1)	
Seldom	672 (55.9)	
Never	302 (25.1)	
Job satisfaction		
Very satisfied	283 (23.5)	
Satisfied	621 (51.6)	
Neither satisfied nor dissatisfied	218 (18.1)	
Dissatisfied	72 (6.0)	
Very dissatisfied	9 (0.8)	

BMI, body mass index; GED, General Education Development.

mellitus (*n* = 64, 5.3%). The BMIs averaged 29.5 ± 6.8 kg/m^2. The population's disorders (eg, diabetes, thyroid disorders among 6.7%, data not shown) and risks are typical for employed, healthier adult populations.

Psychosocial factors were strongly distributed toward not being depressed and being satisfied with the job. A majority acknowledged being "seldom" depressed (*n* = 672, 55.9%) and being satisfied with the job (*n* = 621, 51.6%).

Measured Strain Index scores averaged 8.7 ± 10.4, signifying a moderate risk on average for musculoskeletal disorders attributable to job physical factors.[57,59,63,95,98–102] By comparison, a Strain Index score of less than 3 is considered safe or low risk and greater than 13.5 as hazardous.95,102 Ten-year Framingham scores averaged 6.4% ± 5.1%.

Bivariate analyses assessed the risk of having one or more MSDs as a function of the Framingham risk scores (Table 2). Relative risks mostly increased across the Framingham score categories, rising to 4.10 (95% confidence interval [CI], 2.44–6.88) among those with a Framingham risk score of 15% or higher. Among those with Framingham risk scores of 15% or higher, the relative risk of two or more disorders was 6.81 (95% CI, 3.77–12.33). Among those with Framingham risk scores of 15% or higher, the relative risk of three or more disorders and four or more disorders were, respectively, 13.51 (95% CI, 5.82–31.37) and 19.08 (95% CI, 4.50–80.81). When assessing relative risks within Framingham risk scores less than 15+%, results similarly rose for increasing numbers of disorders.

Adjustments were made for measured BMIs (which is not included in the Framingham score), job satisfaction, feelings of depression, and measured job physical factors (Strain Index) (Table 3, Fig. 1). The relative risks were reasonably comparable with the unadjusted data (Table 3). These relative risks were graphed to help depict the relationships of risk across Framingham risk scores and stratified by an individual's numbers of MSDs (Fig. 1). Trends are present across both variables, such that higher cardiovascular risk scores correspond to increased relative risk for each MSD. As individuals sustain higher numbers of MSDs, a remarkably stronger relationship ensues. Every comparison with the referent group was statistically significant.

DISCUSSION

Cardiovascular disease risk factors strongly predict the risk of developing carpal tunnel syndrome, lateral epicondylopathy, medial epicondylopathy, and rotator cuff tendinopathy. The adjusted relative risk for one or more MSDs increased to 3.9-fold among those with a 10-year Framingham cardiovascular risk score of at least 15%. Risks were far higher among those with subsequently greater numbers of disorders. Among those with four or more disorders, relative risks exceeded 17 in CVD risk categories of both 12% to 14% and 15% or higher. These results support CVD risk factors as presumptively true risk factors for these MSDs.

Naturally, these findings raise many additional questions. One such question is the pathophysiology of this potential disease mechanism. Prior research suggests that this answer is likely best investigated in the rotator cuff. Rothman and Parke[103] and Rudzki et al[104] quantified the poor blood supply to the rotator cuff tendons and found the hypovascular area to primarily affect the supraspinatus tendon in the area of a typical rupture, although there is a secondary neovascularization response that occurs among those with tendinopathy.[105] A quantified microcirculation study reported an 81% reduction in the functional capillary density in the edge of a degenerative rotator cuff lesion compared with control tissue.[106] Subsequent studies suggested that individual CVD risks, such as tobacco and obesity, are associated with rotator cuff tears.[69,70,72,73,77–79,107] Previously reported baseline

TABLE 2. Unadjusted Risk Over 9 Years for Numbers of Musculoskeletal Disorders Related to Framingham Risk Scores

Framingham Risk Score (95% CI)	≥1 Disorder	≥2 Disorder	≥3 Disorder	≥4 Disorder
Score 0–2	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Score 3–5	2.21* (1.56–3.11)	3.21* (2.08–4.96)	6.16* (3.05–12.46)	8.74* (2.39–31.99)
Score 6–8	2.18* (1.55–3.07)	3.14* (2.04–4.84)	4.59* (2.22–9.52)	6.12* (1.59–23.53)
Score 9–11	2.30* (1.59–3.32)	3.29* (2.08–5.21)	6.47* (3.13–13.40)	7.97* (2.07–30.74)
Score 12–14	3.30* (2.21–4.94)	5.25* (3.24–8.51)	8.80* (4.13–18.77)	16.84* (4.54–62.42)
Score ≥15	4.10* (2.44–6.88)	6.81* (3.77–12.33)	13.51* (5.82–31.37)	19.08* (4.50–80.81)

Disorders include carpal tunnel syndrome, lateral epicondylopathy, medial epicondylopathy, and rotator cuff tendinopathy (up to 8 episodes per person).
*$P < 0.05$.
CI, confidence interval.

TABLE 3. Risk Over 9 Years for Numbers of Musculoskeletal Disorders Related to Framingham Risk Scores Adjusted for BMI, Measured Job Physical Exposure (Strain Index), Job Satisfaction, and Feelings of Depression

Framingham Risk Score	≥1 Disorder	≥2 Disorder	≥3 Disorder	≥4 Disorder
0%–2%	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
3%–5%	2.30* (1.57–3.35)	3.17* (1.97–5.11)	5.74* (2.74–12.02)	8.97* (2.37–34.04)
6%–8%	2.48* (1.70–3.62)	3.64* (2.27–5.84)	5.00* (2.35–10.63)	7.04* (1.79–27.74)
9%–11%	2.41* (1.60–3.62)	3.42* (2.07–5.66)	6.89* (3.22–14.75)	8.75* (2.19–34.95)
12%–14%	3.52* (2.27–5.48)	5.40* (3.19–9.15)	8.93* (4.03–19.79)	17.93* (4.67–68.77)
≥15%	3.90* (2.20–6.90)	6.07* (3.16–11.68)	12.04* (4.88–29.67)	17.40* (3.85–78.62)

Disorders include carpal tunnel syndrome, lateral epicondylopathy, medial epicondylopathy, and rotator cuff tendinopathy (up to 8 disorders per person).
*$P < 0.05$.
BMI, body mass index.

analyses of CVD risk factors and rotator cuff tendinopathy also suggested a significant association,[91] supporting the presumptive mechanism of impaired blood supply to the relatively avascular central zone of the rotator cuff tendons, especially at the supraspinatus tendon.

Although the pathophysiology of both epicondylopathy and carpal tunnel syndrome is somewhat unclear in comparison,[108–111] hypovascularity of the lateral epicondyle in the origin of the extensor mass has been reported along with degenerative changes,[112–115] while decreased extensor carpi radialis brevis muscle blood flow has been reported in lateral epicondylopathy patients.[116] Vascularity of the median nerve in the carpal tunnel has also been implicated in the pathophysiology of carpal tunnel syndrome.[117,118] While CVD risk-related impairment of the blood supply to these relatively hypovascular tissues seems likely, pathophysiological studies to examine this potential disease mechanism are needed.

Relationships between CVD risk factors and microvascular disease(s) elsewhere in the body are likely most strongly developed for diabetes mellitus.[119,120] Evidence also suggests a relationship between dyslipidemia and microvascular disease including chronic renal disease.[120–123] Hypertension has also been implicated in small vessel changes.[124] We hypothesize that reported target tissue hypovascularity causes attrition of the tendons, which sets them up for biomechanical and other factors to result in subsequent tendon thinning, weakness, tendinopathy, and ruptures; we hypothesize similar vascular impairment in the median nerve may result in abnormal, reactive swelling. Our line of research suggests that a combination of CVD risk factors may magnify these microvascular disease changes and that once one has developed one of these musculoskeletal disorders, one is progressively more likely to develop additional disorders, all with a unified pathophysiological mechanism.

We speculate that while this study did not measure inflammatory markers, the results of this study may also be potentially adding to a growing body of evidence that inflammatory markers, which may be related to several diverse diseases, include microvascular and macrovascular disease processes. This has been termed the inflammation of aging hypothesis.[125,126] Disorders linked to this hypothesis include CVD,[126,127] diabetes mellitus,[128] metabolic syndrome,[129] cancer,[130] Alzheimer disease,[131,132] frailty,[133] and cognitive decline.[134,135] Evidence from a large cohort study also supports an association between baseline inflammatory markers and subsequent fractures in the older population.[136] As the MSDs in this study tend to occur years to decades earlier than the above diseases studied, this raises speculative questions regarding whether MSDs may serve as early warning signals for those at high risk for CVD and warrant intensified risk modification intervention in these MSD groups. These results also support future study of CVD risk factor modification and subsequent MSD risk reduction.

Strengths of this study include a fully independent, month-by-month assessment of a population for risks of MSDs, rather than reliance on medical records. This study achieved near-complete datasets

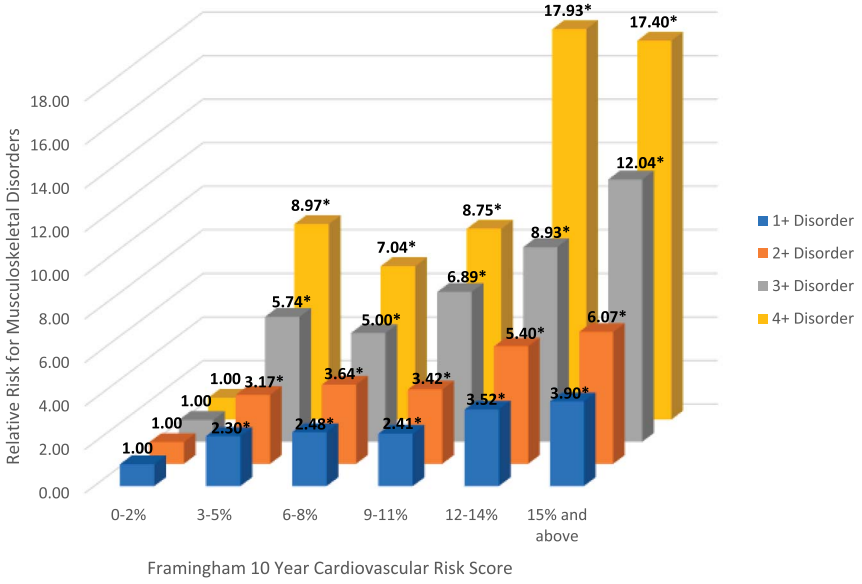

FIGURE 1. Adjusted relative risk for upper extremity musculoskeletal disorders related to Framingham Cardiovascular Risk Score. * Indicates $P < 0.05$, adjusted for BMI, job physical exposure (Strain Index), job satisfaction, and feelings of depression.

by using computerized questionnaires, structured interviews, measured height, measured weights, nerve conduction studies, and standardized physical examinations. Another strength of this study was the ability to adjust for measured job physical factors. This practice is highly unusual, because it is costly to videotape and analyze each job position frame-by-frame to quantify these factors. Teams measuring job factors and health factors were blinded to each other.

There are a few weaknesses of this study, among which is the study design that, while the strongest observational study as a prospective cohort, it is not a randomized study. This study lacked measured lipids among most participants. However, a more precise measure of risk, and consequent reduction in random error, is typically predicted to increase the association for any real relationship, thereby likely strengthening these relationships. We performed an analysis of the subset of participants who had previously measured lipids and also demonstrated a strong relationship. As this study showed major risks, it is predictable that measured lipids would have resulted in increased risk estimates, especially at the higher end of the exposures. Another possible weakness is the use of an occupational cohort; however, the diversity of physical exposures in the study population likely reduces this potential limit to generalizability. Age is included in the Framingham risk score as a robustly weighted factor, and thus indirectly yet strongly incorporated in these analyses; however, it is possible that there may be some residual confounding based on age. As age is strongly incorporated in the overall Framingham risk score, it cannot be included in the regression model because it will introduce structural multicollinearity. It is possible there are other confounder(s), although to negate these findings would require confounder(s) to be both unrecognized and able to cause up to 17-fold risks, which seems improbable. Finally, it is unknown whether the results are generalizable to other common MSDs and whether they are also related to CVD risks (eg, true myotendinous strains, tenosynovitis, trigger digits, nonspecific muscle pain).

Cardiovascular disease risk factors seem to be major risk factors for common MSDs. The higher the 10-year CVD risk estimate, the higher the risk for sustaining at least one MSD. As the CVD risk estimates rise, the risk for sustaining higher numbers of MSDs increases strongly, with up to 17-fold magnitudes of risk among those with at least four musculoskeletal disorders and a 10-year Framingham risk of at least 12%. The increased risk across Framingham scores combined with the risks stratified by numbers of MSDs suggests that these are potent, true risk factors. Thus, further research is needed to confirm these findings, determine whether risk factor modification reduces subsequent risk of another MSD, and identify whether the occurrence of these MSDs signifies increased risks to sustain major cardiovascular events such as myocardial infarction (ie, an early warning system) and thus a subpopulation in need of intensified risk factor management.

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