ORIGINAL RESEARCH

Domains of Physical Activity in Relation to Stiffness Index in the General Population

Natalie Arnold, MD; Arne Deiseroth, MD; Omar Hahad [iD], PhD; Simon Diestelmeier, MD; Andreas Schulz [iD], MD; Andrea Daubenbüchel, MSc; Tommaso Gori, MD; Harald Binder, PhD; Norbert Pfeiffer [iD], MD; Jürgen Prochaska [iD], MD; Manfred Beutel [iD], MD; Karl J. Lackner, MD; Thomas Münzel [iD], MD*; Philipp S. Wild, MD*

BACKGROUND: Regular exercise training represents an important modifier of arterial stiffness (AS). Therefore, sex-specific relations between domains of physical activity (PA; commuting, domestic, and leisure-time PA, including active sport and occupational PA) with AS were investigated.

METHODS AND RESULTS: Stiffness index by digital photoplethysmography was investigated in 12 650 subjects from the GHS (Gutenberg Health Study). Self-reported PA was evaluated by the "Short Questionnaire to Assess Health-Enhancing Physical Activity" and reported as activity score peer week, being a combined measure of duration, frequency, and intensity of PA. Multivariable linear regression analysis demonstrated strong beneficial effects of repetitive activities, such as active commuting or leisure-time PA–related walking on AS in men, but not in women. Lower AS associated with endurance training was also found among men and premenopausal women. In contrast, intense occupational PA was related to stiffer vessels in men ($P<0.0001$) and women ($P=0.0021$) in a fully adjusted model. Combination of both, performing endurance training and having stiffness index values below median, resulted in the best survival. In contrast, subjects with elevated stiffness index at baseline without any endurance activities demonstrated the worst survival.

CONCLUSIONS: In this population representative sample, a differential impact of domains of self-reported PA on AS was demonstrated. Our data strengthen the importance of regular endurance PA to induce a reduction of AS, which, in turn, may improve cardiovascular prognosis. We also report deleterious effects of intense occupational PA on stiffness index, a finding that needs further confirmation by larger prospective trials.

Key Words: arterial compliance ■ mortality ■ physical activity ■ population based ■ stiffness index

It is well established that physical activity (PA) is associated with reduced risk for cardiovascular and total mortality.[1] One possible physiological mechanism underlying such risk reduction might be related to favorable effects of exercise on vascular compliance and remodeling.[2,3] Indeed, experimental data demonstrated a decreased production of several proinflammatory cytokines or activation of potent vasodilating factors (eg, nitric oxide or natriuretic peptide)[4,5] in response to regular exercise. Furthermore, exercise training caused a reduction in total collagen and higher elastin content in hypertensive rats compared with physically inactive animals.[6] The beneficial effects of endurance training on arterial stiffness (AS) have been also consistently reported in clinical settings. Such evidence was established, however, mainly by interventional studies, which were conducted predominantly in male population within several preselected groups (eg, young healthy subjects, in pre/hypertensive individuals, or in subjects with cardiometabolic disorders[7–10]) and reported

CLINICAL PERSPECTIVE

What Is New?

- Lower arterial stiffness was associated with sports-related endurance activities, but also with active commuting.
- Physical activities associated with intense work, such as heavy occupational activity, possessed unfavorable effects on vasculature, reflected by higher arterial stiffness in both men and women.
- Combination of both, performing endurance training and having arterial stiffness values below median, resulted in the best survival over 8 years.

What Are the Clinical Implications?

- There is a differential impact of various domains of physical activity on arterial compliance, which translates into differential cardiovascular risk.
- The present results may provide a basis for more accurate reception of physical activity in the setting of cardiovascular disease prevention.

Nonstandard Abbreviations and Acronyms

AS	arterial stiffness
GHS	Gutenberg Health Study
LTPA	leisure-time physical activity
OPA	occupational physical activity
PA	physical activity
SI	stiffness index
SQUASH	Short Questionnaire to Assess Health-Enhancing Physical Activity

short-term rather than long-term effects of endurance activity. With regard to the general population, the vast majority of published studies to date were focusing solely on leisure-time PA (LTPA) (including active sport)[11–14] with only limited sex-specific data. There is less research published on the role of nonleisure forms of PA, such as active commuting and domestic or occupational PA (OPA), on arterial compliance. Finally, little is known about the relation of exercise to arterial stiffening (eg, as assessed by digital photoplethysmography, because all previous studies have been based on the measurement of pulse wave velocity or wave reflection).[7–14]

Therefore, within the population-based GHS (Gutenberg Health Study), we sought to investigate cross-sectionally the sex-specific association between AS, assessed by stiffness index (SI) obtained from digital photoplethysmography measurements, and 4 main domains of self-reported PA (ie, commuting and LTPA, including active sport, household [domestic], and OPA) using the "Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH)."

METHODS

Data Disclosure Statement

The analysis presents clinical data of a large-scale population-based cohort with ongoing follow-up examinations. This project constitutes a major scientific effort with high methodological standards and detailed guidelines for analysis and publication to ensure scientific analyses on the highest level. Therefore, data are not made available for the scientific community outside the established and controlled workflows and algorithms. To meet the general idea of verification and reproducibility of scientific findings, we offer access to data at the local database in accordance with the ethics vote on request at any time. The GHS steering committee, which comprises a member of each involved department and the head of the GHS, convenes once a month. The steering committee decides on internal and external access of researchers and use of the data and biomaterials based on a research proposal to be supplied by the researcher. Interested researchers make their requests to the head of the GHS (Philipp S. Wild, philipp.wild@unimedizin-mainz.de).

Study Design and Population

The GHS (n=15 010) represents a population-based, prospective, observational, single-center cohort study from western Germany (city of Mainz and County Mainz/Bingen). Details of the study design have been reported elsewhere.[15] Briefly, individuals aged between 35 and 74 years were randomly selected from the local residents' registration office. Sample stratification for sex and present residence (urban/rural) 1:1 was undertaken with equal strata for decades of age. Participation was voluntary, and written informed consent was obtained from each subject on entry into the study. The study was approved by the local ethics committee and data safety commissioner; the sampling design was approved by the federal data safety commissioner.

The present analysis was based on data of 12 650 GHS participants because of technical and logistic constraints (n=1074 with stiff arteries, and n=1286 attributable to logistic reasons [no measurements conducted]). All-cause mortality during a median follow-up time of 10.6 years was chosen as an outcome for the present analysis. Death was ascertained by the respective entry in the registry office and the death certificate. For 833 nonsurvivors (568 men/265 women),

complete information on all variables of interest was available.

Assessment of PA

Self-reported PA level was assessed by the SQUASH.[16] Participants were asked to refer about their regular PA during an average week over the past year. The SQUASH contains questions related to 4 common domains of PA, such as commuting activities, housework (domestic) activities, leisure-time activities (including active sport), and activities at work (ie, OPA). Further structuring for subdomains was done, as reported in Table S1. For the most domains of PA (commuting, leisure-time activities, and sports activities), the main queries of frequency (days per week), duration (average time per day), and effort (light/moderate/intense) were included, whereas domestic activity associated with household and occupational activity was subdivided only into light or intense activity. Furthermore, for occupational activity only, average time (hours) per week was reported. Each domain of PA was assigned a metabolic equivalent value, according to the Ainsworth compendium of physical activities.[17] In addition, an intensity score (range, 1–9),[16] being a combination of subjectively reported effort in the questionnaire with the activity intensity classification, according to Ainsworth's Compendium,[17] as well as the total minutes of activity peer week (in min/wk: frequency [d/wk]×duration [min/d]) were calculated. That led to a further assessment of activity score per week (reported as total minutes of activity per week×intensity score), which was used as a measure of PA within the present analysis. The activity score was calculated for each domain as well as a total activity score as the sum of the activity scores of all domains.

Assessment of AS

SI was assessed by digital photoplethysmography (PCA2 device; Carefusion) and used as a measure for systemic AS. Detailed description of this method has been provided recently.[15] Briefly, a volume pulse waveform with an early systolic and a second diastolic/reflected peak was recorded by transmission of an infrared light through the finger pulp. SI was calculated as the subject's height (meters) divided by time difference between these 2 peaks (so-called "peak-to-peak time") in seconds. All measurements were done in accordance with standard operating procedures with device calibration and subsequent quality control. The intraclass correlation coefficient for assessment of peak-to-peak time and SI, in healthy subjects (n=9), showed a strong agreement of 2

successive measurements in 1-week intervals (peak-to-peak time, 0.92 [95% CI, 0.69–0.98]; and SI, 0.91 [95% CI, 0.65–0.98]).

Data Collection and Definitions of Cardiovascular Risk Factors

Most aspects of data collection and definitions of cardiovascular risk factors have been reported elsewhere.[15] For additional details and for detailed description of statistical analyses, please see Data S1.

Statistical Analysis

For the present analysis, a cross-sectional design (assessing relationship between AS and PA) was combined with a longitudinal design (survival analysis).

All analyses were conducted sex-specifically. Demographic characteristics of the study participants are reported in a descriptive way. The categorical variables are presented by their absolute and relative frequency. Total activity score was categorized into quartiles of its distribution, and Jonckheere trend test was applied. Linear regression analysis with several levels of adjustment was used to assess the relationship between SI (dependent variable) and domain-specific activity score (used as continuous trait per 1000-unit increase in activity score per week). Only exception was "endurance training" (yes/no) and represents a subgroup analysis of 1325 men/1661 women, who reported endurance training only during active sport. Results are reported as βs with their 95% CIs.

Kaplan-Meier survival analysis was performed to evaluate the combined effect of SI and PA on all-cause mortality. Differences in Kaplan-Meier mortality curves were assessed using the log-rank test. All statistical analyses were performed using R version 3.2.2 software (http://www.r-project.org).

RESULTS

The demographic and clinical characteristics of GHS participants have been reported elsewhere. Briefly, data from 12 650 subjects (6578 men/6072 women) were used for the present analysis (Table 1). Almost all traditional cardiovascular disease (CVD) risk factors were more prevalent among men than women. SI was also markedly higher in men than in women, being 8.25 m/s versus 6.28 m/s, respectively. About 20% of study participants reported active commuting, and 66.6% of men and 59.5% of women were performing OPA. Active sport was more frequently reported among women (59.8%) than men (51.4%). More women were also involved in domestic PA (96.9% versus 76.1% among men). The total activity score per week, being a combined measure of duration,

Table 1. Sex-Specific Characteristics of the Study Participants (n=12 650)

Characteristics	Men	Women
Total No.	6578	6072
Age, y	54.0 (45.0/64.0)	53.0 (44.0/63.0)
Body mass index, kg/m^2	27.2 (24.9/30.1)	25.6 (22.8/29.6)
Systolic blood pressure, mm Hg	132 (122/142)	125 (114/138)
Diastolic blood pressure, mm Hg	83.5 (77.5/89.5)	80.5 (74.5/86.5)
Diabetes mellitus, %	10.4	6.8
Hypertension, %	52.7	41.3
Smoking, %	20.8	18.2
Obesity, %	25.7	23.3
Dyslipidemia, %	36.5	21.1
FH of MI/stroke, %	20.5	23.8
Commuting activity, %	19.3	20.0
Leisure-time physical activity, %	93.7	94.4
Active sport, %	51.4	59.8
Domestic activity, %	76.1	96.9
Occupational activity, %	66.6	59.5
Total activity score per week, units*	7189 (4680/9480)	7158 (5160/9267)
Stiffness index, m/s	8.25 (6.35/9.97)	6.28 (5.32/7.73)

Data are expressed as percentage for normally distributed variables or as median (quartile 1/quartile 3), if markedly skewed. FH indicates family history; and MI, myocardial infarction.

*n=9596.

frequency, and intensity of PA, was almost identical between both sexes (7189 in men/7158 in women). However, if the domain-specific activity scores were considered (Table 2), meaningful sex differences in score distribution were observed for active sport and OPA, with higher values in men. In contrast, activity score related to housework was 3-fold higher in women than in men. Although activity scores related to walking or bicycling during LTPA were comparable, there were considerable differences in time spent for each activity, being 2.7-fold higher for walking than for bicycling. The same was true for light and intense OPA, where even 3.8-fold more time spent for light OPA was observed, despite only marginal differences in activity score, thereby suggesting higher work intensity during shorter time for heavy OPA.

The association between PA and AS was further explored by multivariable linear regression analysis (Table 3). In the first step, we assessed a relationship of each domain of PA with SI after adjustment for age (model 1); after adjustment for age, CVD risk factors, and interaction terms (model 2); and after additional adjustment for socioeconomic status and menopausal status in women (model 3). Interestingly, various domains of PA were differentially associated with SI, and such effects were sex specific. For instance, among men, repetitive activities were related to lower AS. So,

Table 2. Sex-Specific Distribution of Different Domains of PA Among Study Participants (n=12 650)

Domains of Activity	Total No.* Men	Total No.* Women	Missing, No. Overall	Activity Score per Week, Median (Quartile 1/Quartile 3) Men	Activity Score per Week, Median (Quartile 1/Quartile 3) Women	Activity Score per Week, 99th Percentile Men	Activity Score per Week, 99th Percentile Women	Duration, Median (Quartile 1/Quartile 3), min/wk Men	Duration, Median (Quartile 1/Quartile 3), min/wk Women
Commuting	1216	1156	688	150 (50/360)	105 (50/250)	2310	1440	75 (35/125)	60 (30/100)
LTPA									
Walking	4988	4701	1557	210 (90/420)	240 (120/510)	2160	2310	180 (90/360)	210 (120/420)
Bicycling	2998	2521	955	300 (150/675)	320 (150/600)	3150	3190	75 (30/150)	75 (30/140)
Gardening	4435	3589	1447	840 (360/1800)	600 (300/1200)	11 300	5970	180 (90/360)	120 (60/240)
Sedentary	5284	4848	1948	1050 (675/1680)	1050 (630/1,55)	5880	5460	1050 (630/1470)	1050 (630/1470)
Active sport	3034	3173	1759	1140 (600/1950)	780 (375/1440)	7270	5590	202 (120/351)	180 (105/300)
Domestic	4761	5387	688	840 (420/1560)	2520 (1470/4080)	5040	11 500	330 (180/600)	1035 (600/1680)
Occupational									
Light	3809	3227	873	4800 (3600/5400)	3480 (2100/4800)	8400	7200	2400 (1800/2700)	1740 (1050/2400)
Intense	1342	795	442	4500 (1500/10 500)	2700 (600/6000)	19 900	15 000	900 (300/2100)	540 (120/1800)

LTPA indicates leisure-time PA; and PA, physical activity.

*For available activity score.

walking during LTPA possessed a beneficial effect on vasculature, with 0.15 m/s lower SI per 1000-unit increase in activity score per week in a fully adjusted model. Inverse relationship between active sport and SI was also observed, and such estimates were more prominent among subsample of subjects, reporting endurance training only: regular endurance exercise was favorably associated with AS in a fully adjusted model with a β estimate of −0.18 (95% CI, −0.32 to −0.04; P=0.0095; dichotomous yes versus no). Active commuting was also inversely related to SI (β, −0.27 [95% CI, −0.51 to −0.03; P=0.025]) in a fully adjusted model.

An oppositional relation with SI was demonstrated for activities, associated with intense work among both sexes. So, 1000-unit higher activity score per week associated with heavy OPA was related to 0.05-m/s higher SI (P<0.0001) in men and 0.03-m/s higher SI (P=0.0021) in women after multivariable adjustment. With regard to the remaining domains, negligible associations were found in both men and women.

To ensure that the effect of a particular PA domain on SI was not biased by other types of PA, we conducted a model, where all domains were included simultaneously in addition to age, interaction terms (age*diabetes mellitus and age*hypertension), arterial hypertension, diabetes mellitus, obesity, smoking, dyslipidemia, family history of myocardial infarction/ stroke, sedentary status, and socioeconomic status (Figure 1). We found that the magnitude of association with SI remained unchanged for LTPA-associated
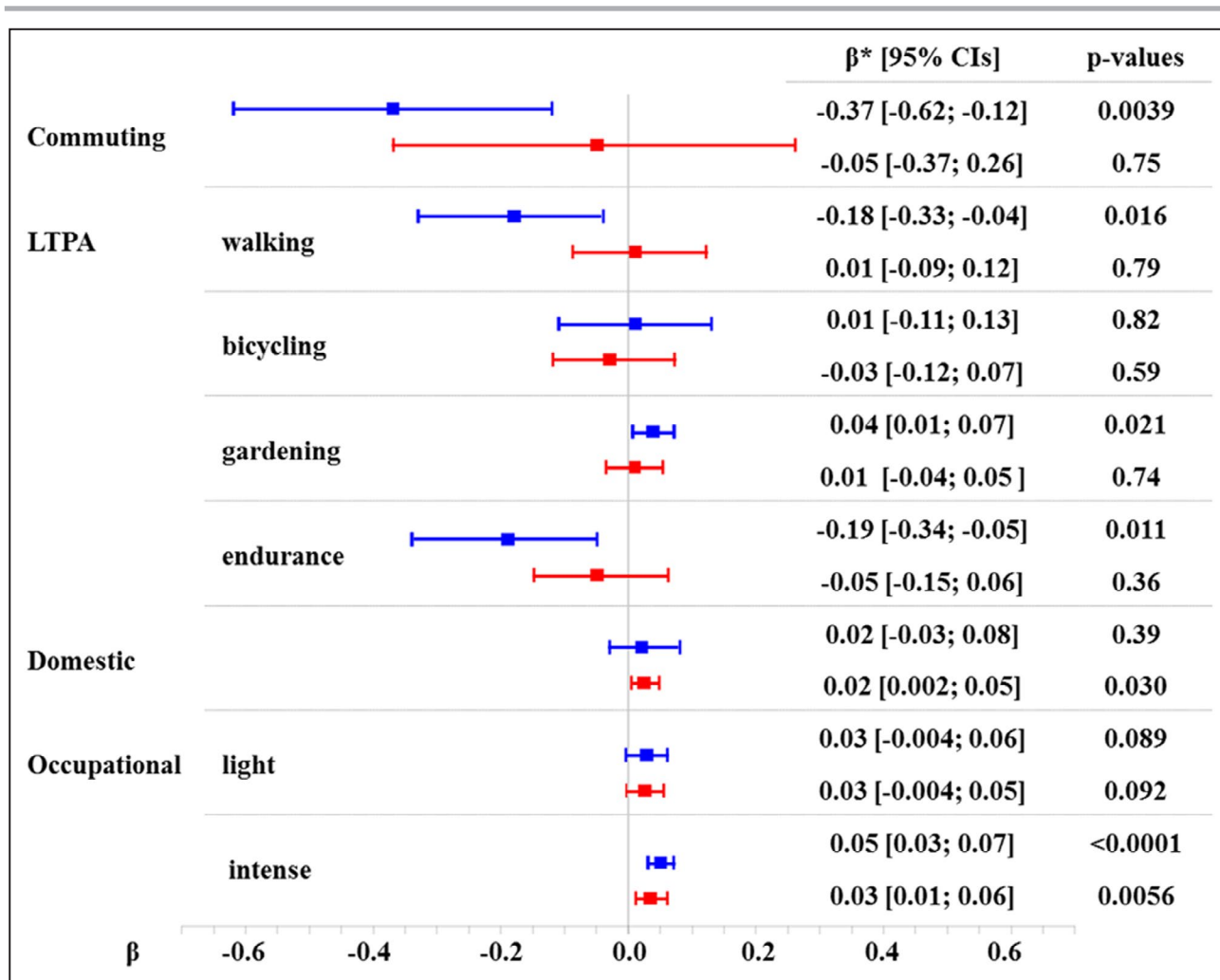
Table 3. SI and PA: Sex-Specific Multivariable Linear Regression Analysis per Domain of PA

Sex	Domains of PA	SI, m/s					
		Model 1		Model 2		Model 3	
		β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value
Men	Commuting	−0.36 (−0.60 to −0.12)	0.0035	−0.27 (−0.51 to −0.038)	0.023	−0.27 (−0.51 to −0.03)	0.025
	LTPA						
	Walking	−0.13 (−0.26 to 0.01)	0.06	−0.13 (−0.26 to −0.004)	0.044	−0.15 (−0.29 to −0.02)	0.021
	Bicycling	−0.08 (−0.17 to 0.01)	0.095	−0.06 (−0.15 to 0.04)	0.23	−0.07 (−0.16 to 0.02)	0.13
	Gardening	0.04 (0.001 to 0.07)	0.02	0.04 (0.006 to 0.06)	0.018	0.03 (−0.003 to 0.06)	0.075
	Sedentary	0.02 (−0.02 to 0.07)	0.34	0.004 (−0.04 to 0.05)	0.85	0.003 (−0.04 to 0.05)	0.90
	Active sport	−0.10 (−0.14 to −0.06)	<0.0001	−0.06 (−0.11 to −0.02)	0.0034	−0.06 (−0.10 to −0.01)	0.011
	Active sport (endurance)*	−0.34 (−0.47 to −0.20)	<0.0001	−0.22 (−0.35 to −0.08)	0.0015	−0.18 (−0.32 to −0.04)	0.0095
	Domestic	−0.01 (−0.06 to 0.04)	0.81	−0.005 (−0.05 to 0.04)	0.85	−0.01 (−0.06 to 0.04)	0.66
	Occupational						
	Light	−0.03 (−0.05 to −0.006)	0.016	−0.02 (−0.05 to 0.001)	0.061	0.00 (−0.03 to 0.03)	0.97
	Intense	0.07 (0.05 to 0.08)	<0.0001	0.05 (0.04 to 0.07)	<0.0001	0.05 (0.03 to 0.06)	<0.0001
Women	Commuting	−0.09 (−0.38 to 0.19)	0.52	−0.05 (−0.34 to 0.23)	0.71	−0.06 (−0.35 to 0.22)	0.66
	LTPA						
	Walking	0.03 (−0.06 to 0.12)	0.47	0.00 (−0.09 to 0.09)	0.99	0.005 (−0.08 to 0.09)	0.91
	Bicycling	−0.02 (−0.10 to 0.07)	0.71	−0.004 (−0.09 to 0.08)	0.92	0.00 (−0.08 to 0.08)	0.99
	Gardening	0.03 (−0.01 to 0.07)	0.12	0.03 (−0.01 to 0.06)	0.18	0.03 (−0.01 to 0.07)	0.17
	Sedentary	0.006 (−0.04 to 0.05)	0.79	−0.003 (−0.04 to 0.04)	0.88	0.00 (−0.04 to 0.04)	0.99
	Active sport	−0.03 (−0.07 to 0.01)	0.19	−0.01 (−0.05 to 0.03)	0.52	−0.02 (−0.06 to 0.03)	0.46
	Active sport (endurance)*	−0.11 (−0.20 to −0.02)	0.020	−0.06 (−0.15 to 0.03)	0.21	−0.07 (−0.16 to 0.03)	0.15
	Domestic	0.01 (−0.01 to 0.03)	0.41	0.01 (−0.006 to 0.03)	0.19	0.01 (−0.006 to 0.03)	0.20
	Occupational						
	Light	0.005 (−0.02 to 0.03)	0.65	0.00 (−0.03 to 0.02)	0.96	−0.004 (−0.03 to 0.02)	0.72
	Intense	0.04 (0.02 to 0.06)	<0.0001	0.03 (0.01 to 0.05)	0.003	0.03 (0.01 to 0.05)	0.0024

SI was used as dependent variable, with a β estimate for 1000−unit increase in activity score per week. The only exception was endurance training, which was treated as a dichotomous variable (yes vs no). Model 1: adjustment for age. Model 2: additional adjustment for hypertension, diabetes mellitus, obesity, smoking, dyslipidemia, family history of myocardial infarction/stroke, and interaction terms (age*diabetes mellitus and age*hypertension). Model 3: additional adjustment for socioeconomic status. In women, additionally adjusted for menopause. LTPA indicates leisure-time PA; PA, physical activity; and SI, stiffness index.

*n=1325 men/1661 women.

Figure 1. Relation between stiffness index and physical activity, according to main domains: sex-specific multivariable linear regression analysis (overall model).

Men in blue; women in red. Stiffness index was used as dependent variable, with a β estimate for 1000-unit increase in activity score per week for different domains (continuously). Only the variable endurance training was used as dichotomous trait (yes vs no). *Model included all above-mentioned domains of physical activity simultaneously and was additionally adjusted for age, interaction terms (age*diabetes mellitus and age*hypertension), hypertension, diabetes mellitus, obesity, smoking, dyslipidemia, family history of myocardial infarction/stroke, physical inactivity, and socioeconomic status. LTPA indicates leisure-time physical activity.

walking and endurance exercise in men as well as for intense OPA in both sexes. The relationship became even stronger between SI and active commuting. Sex specifically, "gardening"-associated LTPA in men and with household work in women became borderline significant.

This analysis was further repeated in women in accordance to their menopausal status (Table S2). Interestingly, intense OPA was related with higher SI in premenopausal women only, whereas a positive association of SI with domestic PA was present only after menopause. More important, a significant lower SI under endurance training was seen in the fully adjusted model among premenopausal women.

To estimate a clinical relevance of regular PA on AS, Kaplan-Meier survival analysis was performed. In total, 833 subjects (568 men/265 women) died from all causes during a median follow-up time of 10.6 years (Figure 2). Combination of both, performing active endurance training and having low SI values (ie, below the median), was related to the best survival. In contrast, subjects with high SI at baseline without any endurance activities demonstrated, as expected, the worst survival. Kaplan-Meier curves for all-cause mortality were also performed according to the distribution of SI and the total activity score categorized as above or equal and below the median. Again, the worst survival was seen in individuals with increased SI and low activity score.
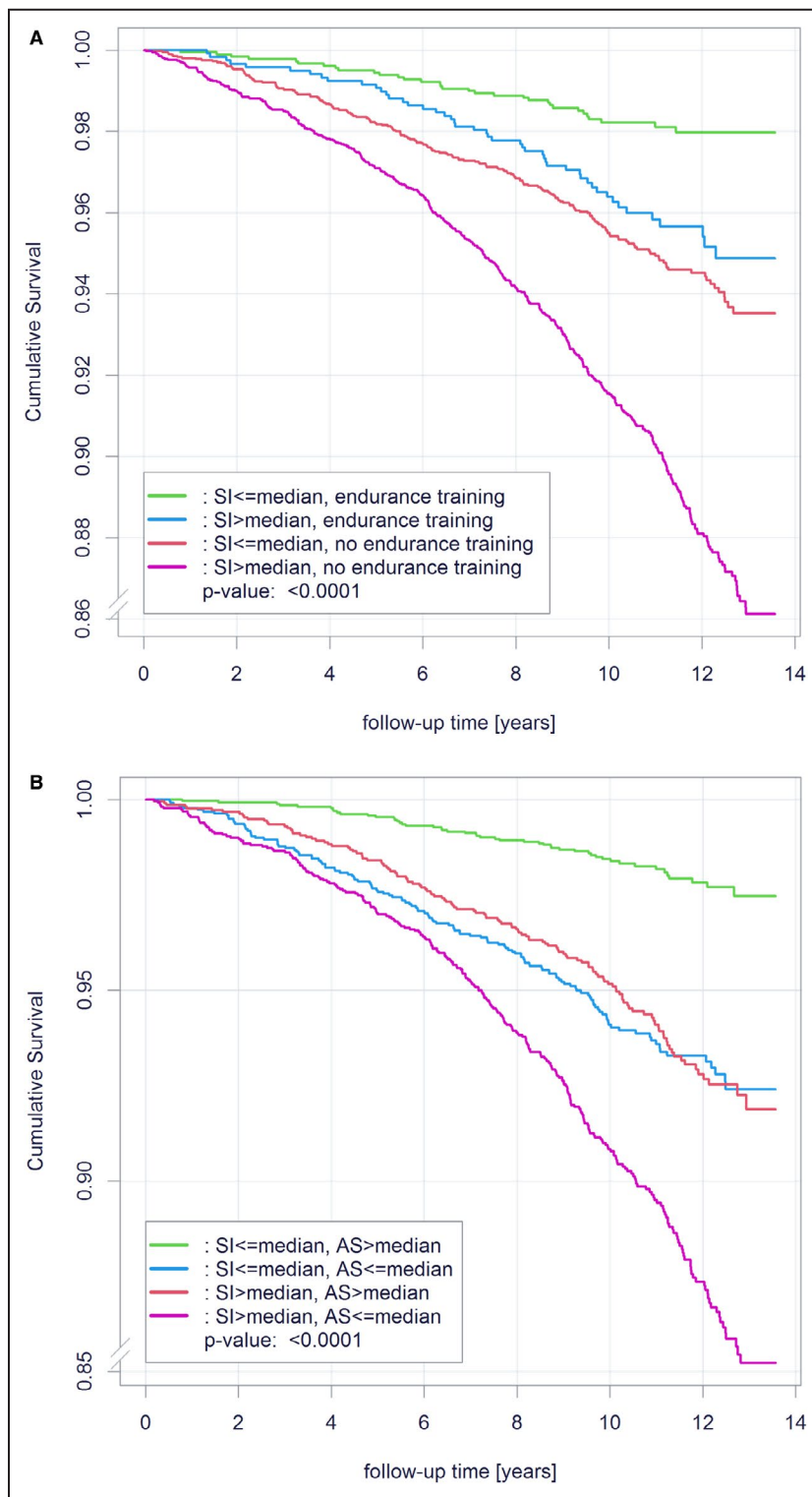
Figure 2.   Impact of stiffness index (SI) and physical activity on cumulative survival.

The panels display Kaplan-Meier curves for an 8-year follow-up period, according to: SI (according to the values below or equal and above the median) and endurance training (yes vs no) (**A**); and SI and total activity score index (both according to the values below or equal and above the median) (**B**). All-cause mortality is shown during a mean follow-up of 6.85±1.64 years. For 414 nonsurvivors (279 men; 135 women), complete information on all variables of interest was available.

DISCUSSION

The results of the present analysis demonstrated a lower SI under several domains of LTPA in men after multivariable adjustment, including cardiovascular risk profile and socioeconomic status. In women, endurance training positively affected arterial compliance in premenopausal subjects only. Furthermore, activities associated with intense work, such as heavy occupational activity, were associated with unfavorable effects on vasculature, reflected by higher AS in both sexes. This analysis represents one of the largest epidemiological investigations to date relating SI (derived from digital photoplethysmography) with simultaneously assessed 4 main domains of PA in the general population.

Exercise and Arterial Compliance

The most important findings from the present analysis were that lower AS was not only associated with sports-related endurance activities, but also with active commuting. To the best of our knowledge, a favorable effect of PA, associated with active transportation to/from work on AS, has not yet been reported. To date, active commuting has been considered as an important tool to increase overall PA level. Protective effects of active transportation on CVD outcome have been already reported with an overall 11% reduction of future cardiovascular risk.[18] Furthermore, the more favorable cardiovascular risk factor profile has been found among those who were physically active for transportation.[19–21] Assuming that traditional cardiovascular risk factors are associated with increased AS,[22] one might speculate that an improved cardiovascular risk profile by PA may lead to increased arterial elasticity. In the present analysis, however, the association between self-reported active commuting and SI existed even after controlling for traditional risk factors and socioeconomic status, suggesting independent effects of commuting activity on SI.

Numerous clinical trials indicated that endurance training is an effective tool for the improvement of arterial compliance (for meta-analysis of 42 interventional studies, including 1627 participants, please see study by Ashor et al[9]), an effect that is secondary to increased vascular nitric oxide and decreased reactive oxygen species production.[23]

Although the present investigation was based mainly on the self-reported data from a population-based study and not from a randomized controlled trial, we also established a lower SI among men and premenopausal women in response to isolated endurance training over the past year.

The differential effects of walking versus bicycling during leisure time on SI identified within the present analysis are intriguing and need further consideration, because a significant favorable association with AS was observed for walking, but not for bicycling. Although the activity scores for walking and bicycling for LTPA were similar, there was a marked difference in time spent for walking compared with that for bicycling (190 versus 70 min/wk at average, respectively), thus pointing to the importance of duration rather than intensity of exercise. Interestingly, current European Society of Cardiology guidelines on CVD prevention[24] recommend at least 150 min/wk exercise of moderate intensity (eg, brisk walking) to healthy adults of all ages. In case our results on favorable SI in LTPA-related walking will be confirmed by future studies with objectively measured PA, this observation would have a significant public health implication, because encouraging people (especially older subjects) to walk might be easier than performing training at vigorous intensity levels.

Interestingly, effects of several domains of PA in women differed clearly from those found among men. Only sport-related endurance training was related with lower SI in premenopausal women, whereas this relation was not present in postmenopausal women, which might be explained by favorable effects of estrogens on vasculature.[25] In general, sex differences in physiological features of exercise are well known[26] and related to differences in function and morphological features of the pulmonary (eg, predisposition to exercise-induced arterial hypoxemia attributable to smaller diameter conducting airways or lung size in women[27]) or cardiovascular (eg, different cardiac structure and hemodynamic response to exercise[28]) system. In addition, changes in substrate metabolism during endurance exercise with higher carbohydrate oxidation rate in men and preferable lipid use in women might also contribute to such disparities.[29] However, whether these differences are responsible for the observed sex-specific relations between PA and SI in the GHS remains unclear.

A further major observation of the present analysis represents a worse arterial compliance in response to heavy OPA in both sexes. This association represents an important finding from a public and occupational health perspective. Several reports indicated that heavy OPA might result in premature death and increased risk for CVD morbidity and mortality.[30–32] Chronic overload of the cardiovascular system, with only limited compensatory time for restitution, is currently considered as a possible mechanism for such detrimental effects of OPA.[33] Furthermore, heavy lifting, static postures, or working with hands above shoulder during intense OPA are associated with both acute increase in blood pressure with initiation of arterial wall shear stress[34] and sustained increased systolic blood pressure not only during work but also at leisure time.[35] Interestingly, arterial hypertension during weight

lifting has also been demonstrated to cause endothelial dysfunction in nonathletes, which might be mediated, at least in part, by decreased vascular nitric oxide bioavailability[36] (eg, attributable to increased vascular superoxide production).

Our finding on increased AS in relation with heavy physically demanding work might further shed light on the pathogenesis of OPA-related cardiovascular events, introducing an additional mechanism behind such association. Indeed, higher AS might affect coronary blood flow by decreasing diastolic blood pressure with consequent reduction of coronary perfusion and predisposition to myocardial ischemia,[37] even in the absence of coronary narrowing. Nonetheless, present results should be interpreted with caution, because they were based on self-reported OPA using a short questionnaire. Unfortunately, other important determinants/correlates of OPA were not assessed by SQUASH. Therefore, incomplete control for these confounders or even exposure misclassification could not be ruled out. Otherwise, the relation between heavy OPA and SI remained consistent and the strongest association, even after adjustment for cardiovascular risk factors, socioeconomic status, and other domains of PA. More important, the 99th percentile of activity score per week, related to heavy OPA, was ≈20 000 in men and 15 000 in women. This implies that, in these subjects, up to a 1.2-m/s higher SI could be awaited, and such substantial difference in AS will translate into an increased cardiovascular risk. These hypothesis-generating results provide an important basis for further investigations on increased AS as a possible pathophysiological consequence of physically demanding work.

Strengths and Limitations

There are limitations that need to be addressed: a causal relationship between PA and AS could not be assessed because of the cross-sectional design of this study. Only self-reported PA was assessed within the GHS, which might be more susceptible to recall or other information bias (eg, social desirability),[38] and the degree of bias may differ between men and women. In addition, habitual PA is better represented by cardiorespiratory fitness than by self-reported PA.[38] However, according to the "decision matrix guide for selecting a PA measurement instrument," proposed by the American Heart Association scientific statement on the assessment of PA,[39] the choice of a questionnaire as assessment method seems to be appropriate within the present population-based analysis because of the sample size. In addition, SQUASH represents a well-established questionnaire, which is widely used in epidemiologic studies because of its practicability: it takes only 3 to 5 minutes to complete and has a fair reliability (r=0.58).[16] Nonetheless, we cannot exclude that observed effects are partly biased by the self-assessment of PA, which led to some imprecision in data assessment.

This study also has several strengths: The GHS is the largest study to date, assessing simultaneously the sex-specific relation of main domains of PA with arterial compliance. Furthermore, this study differs from previous investigations by its detailed coverage of PA not only in commuting, household, occupational, or leisure-time and sports-related activities, but also in their subdomains. This allowed us to gain deeper insight into differential influence of various exercise modalities on SI. Another strength consists in the application of an activity score as a measure of PA, because it represents a combined measure of intensity, duration, and frequency of regular PA during an average week, thereby providing more accurate estimates of absolute amounts of activity or energy expenditure than metabolic equivalent values alone. Finally, long-term rather than short-term effects of different domains of PA on SI were assessed, because participants were asked to report their regular activity over the past year.

Summary and Conclusions

In a representative sample from the general population, a differential relation of domains of self-reported PA on arterial compliance was demonstrated. The findings support previous studies of favorable impact of leisure-time exercise on AS and extend them to active commuting, but also suggest detrimental effects of vigorous OPA. Capturing different major domains of PA may be a more appropriate approach to quantify the impact of exercise on vasculature than assessing only an overall measure of PA. These findings should be further explored because they might have important clinical implications in the future.

Affiliations

Department of Cardiology, Cardiology I, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany (N.A., O.H., S.D., T.G., J.P., T.M., P.S.W.); Department of Cardiology, Preventive Cardiology and Preventive Medicine, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany (N.A., A.S., A.D., J.P., P.S.W.); DZHK (German Center for Cardiovascular Research), Partner Site Rhine-Main, Mainz, Germany (N.A., O.H., S.D., T.G., J.P., K.J.L., T.M., P.S.W.); Department of Sport, Exercise and Health, University of Basel, Switzerland (A.D.); Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany (H.B.); Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Germany (H.B.); Department of Ophthalmology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany (N.P.); Center for Thrombosis and Hemostasis, University Medical Center of the Johannes-Gutenberg University Mainz, Mainz, Germany (J.P., P.S.W.); Department of

Supplementary Material

Data S1
Table S1–S2

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Supplemental Material

Data S1.

Supplemental Methods

<u>Data collection and definition of cardiovascular risk factors and diseases</u>

All study participants underwent a standardized computer-assisted personal interview carried out by a specially trained team of interviewers. Moreover, all subjects participated in a 5-hour baseline-examination at the study center, which was performed according to standard operating procedures by certified medical technical assistants. All measurement procedures have been described in detail elsewhere (15). Hypertension was diagnosed, if antihypertensive drugs were taken, or a mean examination systolic blood pressure of ≥140mmHg or a mean diastolic blood pressure of ≥90mmHg (averaging the 2nd and 3rd standardized measurements after 8 and 11 minutes of rest). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (both measured). Obesity was defined as a BMI ≥30 kg/m^2. Smoking behavior was dichotomized into non-smoking (never or former smokers) and smoking (occasional and daily smokers). Subjects with a LDL/HDL-ratio of >3.5 or with diagnosis of dyslipidemia by general practitioners were classified as having dyslipidemia. A positive family history of myocardial infarction or stroke was recorded in a female first-degree relative ≤65 years or in a male first-degree relative ≤60 years. Diabetes mellitus was defined by already diagnosed or by a blood glucose level of ≥126 mg/dl at the baseline examination after an overnight fast of at least 8 hours, or a blood glucose level of ≥200mg/dl in the baseline examination after a fasting period <8 hours. In addition, those who were on oral blood glucose–lowering therapy or on insulin substitution were also classified as diabetics. Cardiovascular diseases were documented in a computer assisted personal interview by specifically trained and certified interviewers. Participants were asked to bring their medical records and reports to the interview. A disease was recorded as present, if a physician had diagnosed the disease.

Statistical analysis

All analyses were conducted sex-specifically. Demographic characteristics of the study participants are reported in a descriptive way as mean ± standard deviation (SD) for normally distributed continuous variables or as medians with their interquartile ranges, if markedly skewed. The categorical variables are presented by their absolute and relative frequency. Total activity score was categorized into quartiles (Q) of its distribution and Jonckheere trend test was applied. Linear regression analysis was used to assess the relationship between SI (dependent variable) and domain-specific activity score (used as continuous trait per 1000-units increase in activity score per week). Only exception was "endurance training", which was treated as dichotomous variable (yes/no) and represents a subgroup analysis of 1,325 men/1,661 women, who reported endurance training only (e.g. running, jogging, nordic walking etc.) during active sport. In the basic model, adjustment for age was performed. In Model 2 was further adjusted for the traditional CVD risk factors (obesity, dyslipidemia, hypertension, smoking, diabetes mellitus, family history of myocardial infarction/stroke) and for interaction terms (age*diabetes and age*hypertension). Final model included additional adjustment for socioeconomic status (SES); in females. additional adjustment for menopausal status has been also performed. Results are reported as Betas with their 95 % confidence intervals (CIs). At the first step, the relationship between SI and PA was evaluated for each reported domain separately. At the next level, we calculated co-called "overall" model, where all PA domains were included in the fully adjusted model simultaneously. Such analysis was further repeated among females in accordance to their menopausal status.

Kaplan–Meier survival analysis was performed to evaluate the combined effect of stiffness index and physical activity on all-cause mortality. Stiffness index and total activity score were dichotomized as below/equal or above the median; for endurance training a dichotomization

"endurance exercise yes versus no" was used. Differences in Kaplan–Meier mortality curves were assessed using the log-rank test. Due to explorative nature of the present analysis the strength of association was assessed by p-values, with lower values reflecting stronger evidence for a relevant association. All statistical analyses were performed using R version 3.2.2 software (http://www.r-project.org).

Table S1. Domains of physical activity, assessed by the short questionnaire to assess health enhancing physical activity (SQUASH).

Domains	Substructuring	Example of activity
Commuting	walking or bicycling	to/from work
Leisure-time	walking	walking for recreation, visiting or way to/from store
	bicycling	way to/from store or for visiting
	leisure-time work	gardening or other home activities…
	sedentary	reading, watching TV…
	active sport	-
Domestic	light	cooking, ironing, washing dishes, child care
	intense	vacuuming, scrubbing/mopping floors, walking with heavy shopping bags
Occupational	light	sitting office work or easy work including standing and walking, e.g. a desk job
	intense	regularly lifting heavy objects or heavy manual work

Table S2. Stiffness index and physical activity: results of multivariable linear regression analysis ("overall model") in pre- and postmenopausal women.

Domains of physical activity	β [95% CIs]*	p-value
Premenopausal n=1,597		
Commuting activity	-0.19 [-0.58; 0.19]	0.33
Leisure time PA: walking	-0.04 [-0.21; 0.12]	0.60
Leisure time PA: bicycling	0.13 [-0.03; 0.29]	0.12
Leisure time PA: gardening	-0.01 [-0.09; 0.06]	0.70
Active sport: endurance**	-0.16 [-0.29; -0.03]	0.017
Domestic PA	0.02 [-0.01; 0.04]	0.26
Occupational PA: light	0.04 [-0.001; 0.08]	0.059
Occupational PA: intense	0.04 [0.01; 0.07]	0.0087
Postmenopausal n=2,646		
Commuting activity	0.06 [-0.41; 0.52]	0.82
Leisure time PA: walking	0.04 [-0.09; 0.17]	0.54
Leisure time PA: bicycling	-0.08 [-0.20; 0.05]	0.22
Leisure time PA: gardening	0.01 [-0.05; 0.07]	0.72
Active sport: endurance**	0.02 [-0.13; 0.17]	0.82
Domestic PA	0.04 [0.01; 0.07]	0.022
Occupational PA: light	0.01 [-0.04; 0.05]	0.83
Occupational PA: intense	0.02 [-0.02; 0.06]	0.25

Stiffness index was used as dependent variable.

β estimate for 1000-units increase in activity score peer week.

* Model is additionally adjusted for age, arterial hypertension, diabetes mellitus, obesity, smoking, dyslipidemia, family history of myocardial infarction/stroke, interaction terms (age*diabetes and age*hypertension), sedentary and socioeconomic status.

**endurance was treated as dichotomous variable (yes versus no)

PA stands for physical activity