INTRODUCTION

Atrial fibrillation (AF), the most common cardiac arrhythmia, is known to increase the risk of stroke (up to 5-fold), myocardial infarction, and heart failure [1-3]. The age-adjusted prevalence of AF in men and women in the 2010 Global Burden of Disease Study was estimated as 0.59 and 0.37%, respectively [4]. According to a projection study by Colilla et al. [5], in the US the prevalence of AF will more than double, from 5.2 million in 2010 to 12.1 million cases in 2030.

Favorable effects of physical activity (PA) on diseases such as obesity, hypertension, diabetes mellitus, coronary heart disease, and stroke have been identified [6-9]. However, it is unclear wheth-
er PA contributes to the incidence of AF. In fact, the impact of PA on the risk of AF remains controversial. Numerous studies have explored associations between PA and AF [10-15]. A systematic review and meta-analysis by Kwok et al. [16] indicated no significant association between intense PA and AF. In contrast, another systematic review and meta-analysis by Nielsen et al. [17] reported a significant positive association between long-term vigorous PA and AF, while moderate PA was found to show a potential inverse correlation with AF incidence. These contradictory results may suggest that different types of PA have different effects on AF. Bertoni et al. [18], reported a significant association between both vigorous/moderate and intentional PA and the ankle-brachial index (ABI) in women. Moreover, walking pace, as a measure of the intensity of PA, was negatively associated with intima-media thickness (IMT) and ABI in both men and women. Therefore, it is plausible that the intensity of PA might affect AF.

In this cohort study, we aimed to evaluate the associations of PA types (total, moderate/vigorous, and intentional), as well as walking pace, with AF risk in men and women.

### Table 1. Characteristics of participants stratified by gender, MESA, United States, 2000-2011

| Characteristics                  | Women (n = 3,397) | Men (n = 3,090) | p-value |
|----------------------------------|-------------------|-----------------|---------|
| Age (y)                          | 62.40 ± 0.17      | 62.33 ± 0.18    | 0.78    |
| Body mass index (kg/m²)          | 28.64 ± 0.10      | 27.79 ± 0.07    | <0.001  |
| Total cholesterol (mg/dL)        | 199.80 ± 0.60     | 188.06 ± 0.62   | <0.001  |
| HDL cholesterol (mg/dL)          | 56.32 ± 0.26      | 45.06 ± 0.21    | <0.001  |
| Alcohol, current use             | 1,650 (48.57)     | 1,937 (62.68)   | 0.19    |
| Hypertension                     | 1,590 (46.80)     | 1,334 (43.17)   | 0.003   |
| Race/ethnicity                   |                   |                 | 0.25    |
| White                            | 1,312 (38.62)     | 1,220 (39.48)   |         |
| Chinese                          | 410 (12.07)       | 388 (12.56)     |         |
| Black                            | 936 (27.55)       | 784 (25.37)     |         |
| Hispanic                         | 739 (21.75)       | 698 (22.59)     |         |
| Annual income (US dollar)        |                   |                 | <0.001  |
| <50,000                          | 2,187 (64.38)     | 1,581 (51.16)   |         |
| 50,000-99,999                    | 745 (21.93)       | 868 (28.09)     |         |
| ≥100,000                         | 334 (9.83)        | 527 (17.05)     |         |
| Diabetes                         | 379 (11.15)       | 438 (14.17)     | <0.001  |
| Smoking                          |                   |                 | <0.001  |
| Former                           | 1,009 (29.70)     | 1,390 (44.98)   |         |
| Current                          | 386 (11.36)       | 446 (14.43)     |         |
| Atrial fibrillation              | 95 (2.79)         | 147 (4.75)      | <0.001  |
| Walking pace (mph)               |                   |                 | <0.001  |
| Slow (<2)                        | 1,034 (30.43)     | 764 (24.72)     |         |
| Medium (2-3)                     | 1,710 (50.33)     | 1,546 (50.03)   |         |
| Fast (>3)                        | 650 (19.13)       | 777 (25.14)     |         |
| Physical activity (MET-hr/wk)    |                   |                 |         |
| Total                            | 187.58 ± 1.46     | 186.00 ± 1.74   | 0.48    |
| Moderate/vigorous                | 75.58 ± 1.12      | 96.89 ± 1.57    | <0.001  |
| Intentional                      | 20.44 ± 0.49      | 26.70 ± 0.61    | <0.001  |

Values are presented as number (%) or mean ± standard deviation.

MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent of task; mph, miles per hour (=1.6 km); HDL, high-density lipoprotein.
Physical activity measurements

To measure PA, we used the MESA Typical Week Physical Activity Survey (TWPAS), a self-reported standardized questionnaire that has been validated in a cross-cultural activity participation study [20,21]. The TWPAS was designed to identify PA type and time during a typical week over the month preceding the survey. Various types of PA, including household, yard work, care, transportation, walking, dance, team sports, dual sports, individual activities, conditioning, leisure, and walking pace, were categorized into 3 levels of light, moderate, and heavy effort. The minutes of each activity were summed, converted to hours, and multiplied by metabolic equivalent of tasks (METs) [22].

We created 4 variables. The first was total PA (sum of all items, excluding walking pace). The second was the sum of 2 intensity levels (moderate and vigorous MET-hr/wk) for all items with these levels, except for walking pace. The third variable was created as intentional PA (sum of walking for exercise, sports/dancing, and conditioning MET-hr/wk). The fourth variable was walking pace in miles per hour (mph).

Follow-up and ascertainment of atrial fibrillation

The follow-up period extended from July 15, 2000 through September 30, 2011 (approximation 11 years), and was divided into 5 phases.

Initially, participants with self-reported AF were excluded from enrollment in MESA. Every 9-12 months, each MESA participant or a proxy was contacted to record all hospitalizations. An incident AF event was defined as a clinical modification code of 427.31 (AF) or 427.32 (atrial flutter) based on the International Classification of Diseases, 9th revision (during 2000-2011). Trained staff discarded AF cases associated with open surgery and adjudicated all AF events [23].

Statistical analysis

Three PA measures—namely, total, intentional, and moderate/vigorous PA—were categorized into quartiles. Walking pace was created as a 3-level variable. A Cox proportional hazard (PH) model and an extended Cox model were used to examine the association of PA with AF incidence. Analysis of variance and the chi-square test were used for continuous and categorical variables, respectively. Age was used as the time scale to account for left-truncated survival time. In observational studies (such as MESA), subjects are already at risk for the outcome prior to their study entry. Hence, we used age as the time scale, and the outcome variable was age at event or censorship, which is a method that allows more effective control of age [24].

We generated 3 PA variables and walking pace and sought to investigate their independent associations with AF. For this purpose, 3 models were run. The first model was unadjusted (univariate model). Model 2 was adjusted for income, race, and pack-years of smoking. Model 3 was adjusted for the model 2 variables, as well as body mass index (BMI), alcohol, hypertension, diabetes, and lipid profile (total cholesterol and high-density lipoprotein [HDL]). In model 3, the variable of total PA was adjusted in order to assess the associations of walking pace, intentional PA, and moderate/vigorous PA with AF. A multiplicative interaction term was introduced to examine the possibility of interaction between PA measures and race. All analyses were stratified by gender. To test the PH assumption, the interaction with time and a graphical approach were utilized. In the men stratum, walking pace violated the PH assumption. In the women stratum, total PA violated the PH assumption. Because of this violation, we used the extended Cox (non-PH) model. For walking pace and total PA as non-PH variables in men and women, respectively, the Heaviside function (hv) was applied. For this reason, survival time was examined graphically for both walking pace in men and total PA in women. We noticed that the PH for walking pace survival time on day 800 (2.19 years) could be cut to make 2 hazard ratio (HR) values. However, the threshold for total PA was defined on day 400 (1.09 years). Using a single hv in the extended Cox model, 2 HR values would be applied, with each value considered constant during a fixed time interval. In essence, for walking pace in men, 2 HR values were calculated: the first for observations with a survival time of less than 800 days (2.19 years), and the second for observations with a survival time exceeding or equal to 800 days. Concerning

Table 2. AF by PA measures and walking pace, stratified by gender, MESA, United States, 2000-2011

| PA (MET-hr/wk) | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | No. of participants | No. of AF | | No. of participants | No. of AF | |
| Total | | | | | |
| 5-122 | 778 | 30 | | 844 | 57 | |
| 123-173 | 889 | 33 | | 746 | 33 | |
| 174-233 | 878 | 21 | | 731 | 31 | |
| ≥ 234 | 852 | 11* | | 769 | 26 | |
| Moderate/vigorous | | | | | |
| 0-34 | 936 | 12 | | 693 | 11 | |
| 35-69 | 902 | 11 | | 723 | 16 | |
| 70-139 | 878 | 5 | | 749 | 16 | |
| ≥ 140 | 681 | 3 | | 925 | 16 | |
| Intentional | | | | | |
| None | 851 | 10 | | 671 | 12 | |
| 1-14 | 1,122 | 11 | | 825 | 18 | |
| 15-29 | 651 | 5 | | 628 | 10 | |
| ≥ 30 | 773 | 5 | | 966 | 19 | |
| Walking pace (mph) | | | | | |
| Slow (<2) | 1,034 | 37 | | 764 | 45 | |
| Medium (2-3) | 1,710 | 46 | | 1,546 | 68 | |
| Fast (>3) | 650 | 12 | | 777 | 34 | |

MESA, Multi-Ethnic Study of Atherosclerosis; AF, atrial fibrillation; PA, physical activity; MET, metabolic equivalent of task; mph, miles per hour (= 1.6 km).

*p<0.05 for comparisons across categories.
The descriptive characteristics of the men and women are provided in Table 1. No other statistically significant associations were found between PA and AF for the hv2 in all three models.

In contrast to the lack of any significant association between total PA and AF for women (35-69), moderate/vigorous PA were unassociated with AF in women. Additionally, a higher percentage of men reported a fast walking pace (>3 mph), and the prevalence of diabetes was 3 percent higher (14.7%) in men compared with the reference group of 5-122 MET-hr/wk. As shown, moderate/vigorous and intentional PA were higher in men. Additionally, a higher percentage of men reported both former and current smoking. BMI, total cholesterol, and HDL-cholesterol showed higher values in women.

No other statistically significant associations were found between PA measures and incident AF by gender. Intentional and moderate/vigorous PA were higher in men. Additionally, a higher percentage of men reported both former and current smoking. BMI, total cholesterol, and HDL-cholesterol showed higher values in women.

Table 3 summarizes the association between PA measures and atrial fibrillation, stratified by gender, MESA, United States, 2000-2011.

Table 3. Association between physical activity (MET-hr/wk) measures and atrial fibrillation, stratified by gender, MESA, United States, 2000-2011

| PA | Women | Men |
|----|-------|-----|
|     | 1-14  | 15-29 | ≥30 |
| Model 1<sup>1</sup> | 0.80 (0.34, 1.88) | 0.62 (0.21, 1.81) | 0.51 (0.17, 1.51) | 1.15 (0.55, 2.40) | 0.83 (0.36, 1.93) | 1.05 (0.51, 2.16) |
| Model 2<sup>2</sup> | 0.74 (0.31, 1.77) | 0.57 (0.19, 1.70) | 0.47 (0.16, 1.41) | 1.18 (0.55, 2.53) | 0.91 (0.38, 2.16) | 1.06 (0.49, 2.29) |
| Model 3<sup>3</sup> | 0.69 (0.29, 1.65) | 0.54 (0.18, 1.63) | 0.53 (0.17, 1.66) | 1.28 (0.59, 2.77) | 1.02 (0.42, 2.44) | 1.27 (0.57, 2.83) |
| Moderate/vigorous<sup>4</sup> | 35-69 | 70-139 | ≥234 |
| Model 1<sup>1</sup> | 0.89 (0.39, 2.02) | 0.39 (0.14, 1.13) | 0.31 (0.08, 1.12) | 1.29 (0.60, 2.78) | 0.97 (0.45, 2.11) |
| Model 2<sup>2</sup> | 0.85 (0.37, 1.94) | 0.36 (0.12, 1.04) | 0.38 (0.08, 1.11) | 1.36 (0.62, 3.09) | 1.06 (0.47, 2.38) |
| Model 3<sup>3</sup> | 0.83 (0.34, 2.01) | 0.43 (0.12, 1.50) | 0.46 (0.07, 2.83) | 1.87 (0.72, 4.60) | 2.24 (0.71, 7.08) |
| Total<sup>5</sup> | 123-173 | 174-233 | ≥234 |
| hv1<sup>6</sup> (<400 d survival time) | 0.81 (0.16, 4.06) | 0.81 (0.16, 4.03) | 0.48 (0.17, 1.33) | 0.48 (0.17, 1.33) | 0.07 (0.01, 0.61) | 0.08 (0.01, 0.63) | 0.67 (0.35, 1.31) | 0.51 (0.24, 1.05) | 0.47 (0.22, 0.97) |
| hv2<sup>7</sup> (≥400 d survival time) | 0.70 (0.14, 3.51) | 0.73 (0.14, 3.63) | 0.42 (0.15, 1.17) | 0.42 (0.15, 1.17) | 0.06 (0.01, 0.53) | 0.07 (0.01, 0.57) | 0.69 (0.34, 1.37) | 0.59 (0.24, 1.11) | 0.49 (0.23, 1.05) |
| Model 1<sup>1</sup> | 0.58 (0.11, 2.04) | 0.62 (0.12, 3.13) | 0.40 (0.14, 1.14) | 0.40 (0.14, 1.14) | 0.07 (0.01, 0.56) | 0.07 (0.01, 0.59) | 0.77 (0.38, 1.54) | 0.57 (0.26, 1.25) | 0.59 (0.27, 1.28) |

MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent of task; hv, Heaviside function.

<sup>1</sup>Reference category: no MET-hr/wk.
<sup>2</sup>Model 1 was unadjusted (univariate model).
<sup>3</sup>Model 2 was adjusted for age, income, and pack-years of smoking.
<sup>4</sup>Model 3 was adjusted for model 2 variables plus body mass index, alcohol, hypertension, lipids (total cholesterol, high-density lipoprotein cholesterol), and diabetes.
<sup>5</sup>Reference category: 0-34 MET-hr/wk.
<sup>6</sup>Reference category: 5-122 MET-hr/wk.
<sup>7</sup>hv1: for the observations with a survival time less than 1,200 days (3.28 years).
<sup>8</sup>hv2: for the observations with a survival time exceeding or equal to 1,200 days (3.28 years).
Table 4. Association between walking pace (mph)\(^1\) and atrial fibrillation, stratified by gender, MESA, United States, 2000-2011

|            | Women | | | Men | |
|------------|-------|---|---|-----|---|
|            | Medium (2-3) | Fast (>3) | hv1\(^1\) (< 800 d survival time) | Medium (2-3) | Fast (>3) | hv2\(^2\) (≥ 800 d survival time) |
| Model 1\(^2\) | 0.61 (0.27, 1.33) | 0.72 (0.27, 1.92) | 1.31 (0.61, 2.80) | 0.57 (0.20, 1.62) | 1.17 (0.31, 4.44) | 1.92 (0.49, 7.46) |
| Model 2\(^3\) | 0.59 (0.26, 1.32) | 0.68 (0.24, 1.86) | 1.42 (0.64, 3.16) | 0.61 (0.21, 1.78) | 1.50 (0.31, 7.25) | 2.35 (0.47, 11.73) |
| Model 3\(^4\) | 0.59 (0.26, 1.36) | 0.69 (0.23, 2.00) | 1.67 (0.75, 3.75) | 0.76 (0.26, 2.27) | 1.69 (0.34, 8.22) | 2.85 (0.56, 14.13) |

MESA, Multi-Ethnic Study of Atherosclerosis; mph, miles per hour (= 1.6 km); hv, Heaviside function.
\(^1\)Reference category: slow (<2 mph).
\(^2\)Model 1 was unadjusted (univariate model).
\(^3\)Model 2 was adjusted for race, income, and pack-years of smoking.
\(^4\)Model 3 was adjusted for model 2 variables plus body mass index, alcohol, hypertension, lipids (total cholesterol, high-density lipoprotein cholesterol), and diabetes.

| hv1: for the observations with a survival time less than 800 days (2.19 years).
| hv2: for the observations with a survival time exceeding or equal to 800 days (2.19 years).

The association between walking pace and AF is presented in Table 4. Two HR values for men before and after the point of 800 days were calculated. Walking pace was not associated with AF incidence in all 3 models for hv1 or for hv2. In addition, walking pace did not show a statistically significant association with AF incidence in women.

There was no evidence of multiplicative interaction between the 3 PA measures and walking pace and race/ethnicity in their associations with AF.

**DISCUSSION**

In this prospective analysis, total PA was associated with reduced incident AF in women in the hv2 analysis (equal or exceeding 400 days’ survival time), even after controlling for demographic and lifestyle covariates. A study by Everett et al. [14], showed that PA in women may reduce the risk of AF; however, after controlling for BMI, this relationship disappeared. In our study, walking pace was not associated with AF incidence in women or men.

In a previous study, Bapat et al. [10], working with MESA data after a shorter follow-up (7.7 years), found no independent association between intentional and vigorous PA and the incidence of AF. However, in the vigorous PA subgroup, those with more intentional exercise showed a reduced risk of AF compared with those who did not engage in intentional exercise. Similarly, we did not observe any associations between intentional PA and AF. Our results regarding walking pace among men are in contrast with those of the study conducted by Mozaffarian et al. [15]. They found that walking pace was negatively associated with AF incidence in a study of older adults (≥ 65 years of age). Additionally, Williams & Franklin [11] reported that walking might reduce the risk of AF. They estimated that the risk of AF significantly decreased per MET-hr/d of walking. A systematic review by Zhu et al. [25] revealed that total PA had a direct effect on men and an indirect effect on women. Overall, they reported that PA is likely a risk factor for AF in men and a protective factor against AF in women, respectively. However, they indicated that neither total PA nor intensive PA, regardless of gender, was associated with AF incidence. Cardiac adaptation to PA may be different between men and women. Under comparable and equal conditions, men appear to exhibit deleterious structural remodeling [26]. In addition, compared with men, women produce fewer atrial electrophysiological changes in response to rapid atrial pacing [27]. Exercise is a very important mechanism that may lead to increased parasympathetic tone as a mediator of AF [13]. Moreover, certain mechanisms, regardless of gender, should be considered. Regular PA could disturb the balance between the sympathetic and parasympathetic nervous systems, leading to increased vagal tone, which could result in AF. Increasing the left atrial size is another mechanism that may be involved [28]. It should be noted that PA behavior is different between men and women. According to Keadle et al. [29], men engage in more and more vigorous PA and are more active than women.

Some limitations of the present study are evident. First, measurements of PA were self-reported, potentially leading to measurement bias (misclassification). Second, the power to find associations may not have been adequate, due in part to the presence of asymptomatic AF cases. Therefore, the desirable effects of PA may have been spoiled. Third, competing risk analysis was not applied to account for deaths during the follow-up period. Fourth, the TWPAS was designed to identify PAs and time spent in the typical week one month ago, and this “typical week” does not point to...
only a single time point. Instead, it refers to usual patterns of behavior. Thus, PA is not a momentary and temporary exposure. Additionally, PA is a time-varying variable and most likely changed within the follow-up period. As a result, repeated measurements are needed, and new analytical methods such as the g-formula and g-estimation should be applied.

Nonetheless, this study has some strengths. Using the hv for the predictors that violated the PH assumption improved the precision of our study. In fact, for PHs, it is not logical or permissible to report only a single HR value across the entire follow-up period; instead, it must be split. As another advantage, recruiting subjects belonging to a wide range of age groups (45-84 years) and different categories of race/ethnicity (Caucasian, Asian, African-American, and Hispanic) could enhance the generalizability of the study. In addition, by using adjusted models 2 and 3 (multivariable models), the influence of confounding was attenuated. In essence, confounding could exist because under some circumstances, some participants may increase their PA because of certain factors that increase the risk of AF.

In summary, these results revealed that gender may be an interaction in the association between total PA and AF incidence. Our findings suggest that PA is inversely associated with AF in women.

ACKNOWLEDGEMENTS

This manuscript was prepared using MESA Research Materials obtained from the NHLBI; Research Materials Distribution Agreement (RMDA) V02 1d20120806. We would like to extend our thanks to the staff and coordinators of BioLINCC.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare for this study.

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