Exercise, sex and atrial fibrillation: arrhythmogenesis beyond Y-chromosome?

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Although prevailing research trends favour large clinical trials and registries, meticulous observation during daily clinical practice remains a valuable source for hypothesis generation in medical research. Clinical experience has allowed the identification of several risk factors in the cardiovascular field. For instance, two groups of investigators noticed in parallel that patients with atrial fibrillation (AF) but no cardiovascular disease used to be healthy, fit, heavily trained middle-aged men. By the end of the 1990s' and beginning of the 2000s', a series of articles were published confirming their observations: a history of continued endurance training associated with an increased risk of AF. Initial small case-control and cohort studies almost exclusively included men in order to accurately and homogeneously fit their observations and hypothesis, with women representing only 2% of all patients (Figure). The link between physical activity and AF remained suspicious of bias and was largely disputed in the scientific community until the publication of large epidemiological studies. Similarly to previous small studies, these were initially carried out in men; women were progressively included in subsequent works (Figure). Finally, as evidence of this association had already been firmly established in men, an increasing need to test its validity in women aroused. Two studies exclusively focusing in women recalled initial clinical observations:[1,2] women were not seemingly affected by the AF-risks of exercise.

A work by Drca et al. in this issue of Heart provides novel insights into the association of physical activity and AF in 39,227 women included in the prospective Swedish Mammography cohort.[3] In 1997, participants averaging 60 years old filled a baseline questionnaire assessing time spent in leisure-time physical activity and for transportation purposes. As opposed to previous works,[1,2] participants were also inquired about their recalled exercise habits while young adults at 30 years old. The 12-year period following baseline time-point was reviewed in electronic medical records at the national level to collect AF diagnoses. Their main findings can be summarized around two important ideas.

A first remarkable message from Drca et al. is that ongoing moderate or high-intensity physical activity at 60 years old prevents from AF. With no doubt, this should be an additional, compelling item to add to the backpack of physical activity benefits in the elderly. A 20% decreased risk of AF in the most active group remained after adjusting for several concomitant cardiovascular risk factors. This brings us some food for thought…

Is multivariate adjustment accurate enough in the elderly? Frailty in aged individuals is a quite intuitive concept, but hard to measure and include in a multivariate analysis. More fragile individuals are less likely to exercise; how this under-adjustment of data could have changed final conclusions is unclear.

Should exercise-promoted outcomes be adjusted for cardiovascular risk factors? How should results be interpreted? It is well-known that physical activity improves cardiovascular risk profile, and thus some hypertension- or dyslipidemia-mediated beneficial effects might be lost after multivariate adjustment. Certainly, an adjusted analysis yields important data on the isolated effects of exercise after associated changes in cardiovascular profile have been excluded. However, it is worth noting that the adjusted relative risk is likely underestimating the true benefit of physical activity in the community.

Which are the mechanisms mediating decreased AF incidence after adjusting for cardiovascular risk factors? In addition to an improved cardiovascular risk profile, physical activity is known to associate chronic anti-inflammatory and anti-aging effects. Are these enough to produce such a large 20% decrease in AF incidence in the most active group?

A second conclusion, likely the most challenging one, is that physical activity at 30 years old does not increase AF risk later in the life of women. These results contrast with previous data from the same research group in men.[4] So at this point in time it is becoming quite clear that the well-recognized association of exercise and AF does not apply to women. The reasons underlying different responses to the same stimulus remain obscure. A simple, straightforward answer is that women are, somehow, protected against the deleterious consequences of intense exercise. Indeed, data in the

literature support that cardiac adaptation to physical activity differs in both genders. After a comparable amount of exercise, structural remodeling including left atrial dilation is more intense in male athletes,[5] consistent with experimental data showing an attenuated response to hemodynamic overload in female rats.[6] An acute increase in right atrial pressure does produce less changes in atrial electrophysiology in women than it does in men.[7] On the other hand, some data point to an enhanced atrial proarrhythmogenic substrate in women. Endurance exercise induces a transient, intensity-dependent systemic pro-inflammatory status after exercise bouts that might contribute to atrial deleterious remodeling. Although controversial data has been published, the inflammation cascade might be amplified in women after similar amounts of exercise.[8] Autonomic tone plays a critical role in exercise-induced AF, and a similar training load yields a deeper vagal enhancement in women than in men.[5] Whether the resulting remodeling is similarly arrhythmogenic in men and women still needs to be assessed.

Nevertheless, differences in gender-associated AF risk likely go beyond Y-chromosome susceptibility. Environmental determinants are playing a critical role in exercise-induced AF. Exercise-induced AF is generally diagnosed in patients involved in regular high-intensity endurance activities such as marathon running, cycling and cross-country sky. However, historical circumstances have caused women to be much less engaged in intense training than men. In this regard, marathon running might be seen as a rough estimator of physical activity habits of a population. Data from Drca et al. needs to be placed into context: a simple arithmetic operation shows that women in this study were asked about the leisure-time physical activity habits they were engaged in 1967 (the year at which they were 30 years old). It was in 1967 that Kathrine Switzer became the first woman to *officially* run the Boston Marathon, a year in which 740 male participants had already been registered. In contrast, more than 40% of the 26,610 athletes finishing the Boston Marathon in 2015 were women. These facts provide an estimate of the low leisure-time physical activity burden in women some 50 years ago and how society has evolved since then. Can results derived from 50 years ago be applied today after such a dramatic change?

In June 23rd 2014, *Time* magazine published a polemical cover and inside article entitled "Eat Butter". In this article, the authors suggested that, as US population increasingly feared saturated fat, sugar consumption exponentially increased and initiated an obesity and metabolic syndrome pandemic. Dietary guidelines recommending a reduction in fat ingestion were first published by the US Department of Agriculture in 1980; since then, publicly available data from the Centers for Disease Control and Prevention show that age-adjusted prevalence of obesity (BMI> 30 kg/m^2) has increased from 22.9% to 34.9% and diabetes prevalence raised from 3.7% to 8.5%. This paradoxical response underlines the need for a close follow-up of significant modifications in the population behaviour and their (un-)expected consequences. It is essential to interpret actual data, but we should be able to foresee how their determinants might change over time. Where do we stand now with exercise-induced AF in women? Undoubtedly, women practising as much physical activity as that in the 1960s' are not an increased risk. Are women nowadays running a marathon at risk of AF? The answer is that we do not known, and further data is warranted in the upcoming years. The work by Drca et al. is a much needed departure point for future follow-up studies in which changes in the intensity of exercise will be challenged against data from the 1960s'. Women are now engaged in more regular and more intense physical activity –fortunately. We should definitely keep an eye on it.

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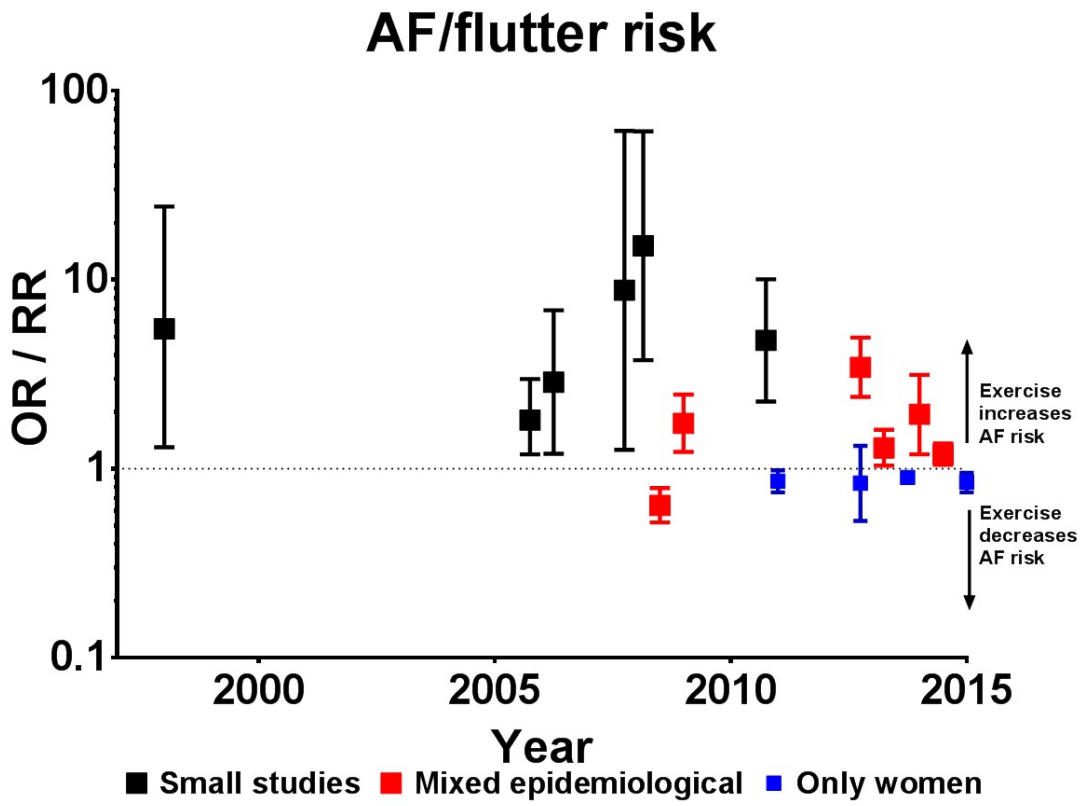
Figure legend

Graphical summary of some representative studies assessing exercise-induced atrial fibrillation risk depending on the gender composition and design of the study. Upper panel: overall percentage of women included for each type of study, from initial small case-control/cohorts studies (<1,000 individuals included) to male/both gender or women-exclusive epidemiological studies (>3,000 individuals). Lower panel: relative risk or odds ratio of exercise-induced AF (sedentary vs the most intense group) in these studies, represented along their publication year and coloured according to the study design. References (S1-S16) of the studies are reported in Online Supplementary Material.



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Note that studies here are identified in the same order (within each study design) as they appear in the Figure.

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Only women epidemiological studies

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