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Physical activity: From epidemiological evidence to individualized patient management

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ABSTRACT

Background: Physical activity (PA), physical fitness (PF), and even a few sedentary behaviors (SB) are strongly and independently linked to improved survival rate. However, key questions remain: what are the physiological interrelationships between SB, PA, and PF? How should we differently emphasize promoting PA, increasing PF with exercise, and decreasing SB among other prevention measures? What are the interrelationships of both PA and SB levels with drug treatment efficacy?
Methods: To address these questions we developed an integrated patient-centric model combining physiology with epidemiological evidence to characterize the individual risk attached to PA level, PF, and SB. Epidemiological data were collected by extensive literature review.
Results: Nine meta-analyses, 198 cohort studies (3.8 million people), and 13 controlled trials were reviewed.

1. A high level of SB induces chronic stress and increases the risk of both chronic disease and mortality.
2. Vigorous PA increases PF and physiological reserve, thereby improving survival rate. This effect is not mediated by improved traditional risk factors.

The risk for most individuals is a mix of high SB, low to mild PA, and low to mild PF.
This model can improve the individualized prescription of PA modalities. Furthermore, the benefit of treatments such as statins or beta-blockers can be cancelled out if a decrease in PA or an increase in SB is induced by drug related side effects.
Conclusions: To improve patient management both types of therapeutic interventions and dose should be carefully chosen for each individual in order to maintain/increase PA level while decreasing SB.

1. Introduction

The worldwide epidemic of low physical activity (PA) [1] underscores the need for physicians to consider PA a main component of their patients' risk. Epidemiological studies have consistently shown that both a high level of PA and a high level of physical fitness (PF) are strongly linked to improved survival rate. Five days per week of at least 30 min of moderate-intensity PA is recommended for adults [2]. Both American and European guidelines on cardiovascular disease prevention recommend measuring PF by exercise testing for risk assessment [3,4]. Finally, a recent European set of recommendations highlights the importance of characteristics and modalities of PA and exercise for cardiovascular health in the general population [5] and in individuals with either CV risk factors [6] or CV disease [7].

However, many practical questions remain, e.g. how much should we emphasize PA compared with other prevention measures? How much should we promote exercise, daily PA, or less sedentary behavior (SB)? What is the impact (if any) of drugs on PA level and how much does it matter? Should we favor pharmacological treatment at clinical-trial-defined optimal dose over preserving or increasing PA level? Surprisingly, PA is usually superseded in priority order by advising pharmacological treatment and nutrition [8] despite weaker evidence supporting the association of dietary factors with mortality.

To address these practical issues we developed a patient-centric model describing the interaction between PA, PF, SB, and an individual's

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risk of premature mortality. Relevant epidemiological evidence was collected by reviewing the literature.

2. Method

2.1. Patient-centric model: objective and requirements

Our main objective is to develop a patient-centric model which integrates epidemiological evidence within a physiological approach. This model should characterize, at the individual level, the lifetime interactions of PA, PF, and SB with mortality risk. PF, a powerful risk predictor, is a fundamental physiological characteristic. PA and SB are two behaviors also linked to premature mortality rate. Interplay between these three components is suspected but should be better characterized.

In order to base our model on solid epidemiological ground, we needed to review epidemiological evidence with a particular interest in the interactions between PA, PF, SB, and mortality rate. We used meta-analyses to quantify these interactions. However, the strength of this quantification is limited in that meta-analyses only take into account the common pieces of information in a limited set of studies. Furthermore, meta-analyses only assess statistical associations between PF, PA, or SB and mortality risk. Interactions between PF, PA, and SB were only taken into account in some studies by using statistical models adjusted for PA or PF whenever measured. Therefore, we needed a more comprehensive approach to collecting information on the interactions between PF, PA, SB, and mortality rate. We conducted an extensive review of published reports on cohort studies and randomized controlled trials evaluating these links (2000–2011), and also conducted a follow-up search up to August, 2013. The objective of the extensive review was both to evaluate the meta-analyses' results' validity in a larger set of populations and to better understand interplay between PA, PA domains, PF, SB, and mortality rate. The objective of the follow-up search was to identify new studies which could substantially modify the results of the previous analysis.

2.2. Literature review

Methodology of the extensive review was very similar to the one required for systematic review, with some adaptations related to the objectives.

2.2.1. Search strategy

MEDLINE databases and the Cochrane database of systematic reviews were searched for English language publications from 2000 to November 1, 2011. Boolean search was used with the key words: “physical activity and/or fitness and mortality”. Citations of interest were independently selected by two reviewers. We also searched the reference list of relevant articles and reviews. Reports selected by at least one reviewer were included and full-texts were analyzed in-depth.

The same databases were regularly searched up to August, 2013 (follow-up search), with review of the titles and abstracts of relevant articles.

2.2.2. Inclusion criteria

Meta-analyses assessing the strength of the links between PF, PA or SB and mortality rate were identified and analyzed.

Prospective cohort studies and randomized studies assessing the links between either PA or PF with mortality were selected for the extensive review. For each report selected from the literature search, the prospective cohort on which the study was run was identified and relevant information was collected either from the report or from other related sources such as publications or websites. Screened reports which did not provide information on mortality rate were used for the identification of the related cohort. Other reports on this related cohort were then searched for mortality data.

Reports identified with the same search strategy during the follow-up search were selected based on title and abstract, and on full-text article if necessary. Relevant pieces of information from these articles were included in the present work, but not in the extensive review.

2.2.3. Data extraction

Data were extracted from the relevant sources including selected reports and related publications. The following data were extracted: name of first author and year, cohort name and characteristics (country, type of population included, type of cohort), number, age, men/women, condition/disease, PA/PA subtypes/PF/SB measurement protocols, follow-up, type of mortality, results (semi-quantitative: positive, negative association, neutral result, trend), gradient effect, and temporal relationships.

2.2.4. Quality assessment

The following data enable a quality assessment of each cohort: whether representative, population-based, or based on disease condition, age and sex distribution, follow-up, type of assessment of PA, PF, or protocol used. Since there is a large discrepancy in adjustment variables across the studies, we chose to base our semi-quantitative analysis on age and sex adjusted models. However, these results were not provided in several studies, so in those cases we used the least adjusted model. Consistency between the several reports on the same cohort was checked.

2.2.5. Publication bias

A formal analysis such as funnel plot is not possible because of the heterogeneity of the results' presentation. As previously described, we tried to identify all the cohorts which collect data on PA, PF or SB through protocol publications and web-sites.

3. Results

We first describe the relevant epidemiological information and then lay out the model's characteristics and its usefulness for patient management.

Nine meta-analyses [9–17], including from 3600 to 980,000 individuals, 198 cohort studies totaling 3.8 million people included in 105 cohorts, and 12 randomized studies were analyzed in depth. Studies' characteristics are summarized in Tables 1 & 2 (details in online supplementary material). Seventy seven reports on cohort studies and one on randomized controlled trial were identified during the follow-up search. Full-texts of these reports were screened and results included if relevant. The Prisma flow diagram is shown in Fig. 1.

3.1. Epidemiological studies have clearly shown that both PF and PA are independently linked to mortality

One metabolic equivalent (MET) increase in PF is associated with a 13% decrease in the risk of premature mortality [13]. Similarly, a recent cohort study found that a one-MET increase in PF during a 12-week cardiac rehabilitation program is associated with a 13% reduction in mortality [18].

Each activity which contributes to PA has an assigned energy expenditure (MET) which is multiplied by the time (h) spent in this activity (Table 3). Both total PA and the various PA domains are associated with lower mortality rate [15], and an inverse relationship between MET-h/week and all-cause mortality rate has been found [16]. This relation appears to be nonlinear with the benefit being greater for 11 MET-h/week of light-to-moderate PA compared with 0 MET-h (19% reduction in the risk of premature mortality), and with a smaller incremental benefit for higher levels of PA: 31 MET-h/week of moderate PA is

Table 1
Characteristics of meta-analyses.

1st author/year	Exposure	Citations identified	Reports included	Individuals (in mortality studies)	Age at inclusion	Follow-up (years)	Results (RR)
Cooper, 2010	Walking speed	2270	28 (1.2%)	14,692	61– >70	3–5	0.35
Davies, 2010	Exercise training (RCT)	11,561	23 (0.2%)	3647	43–72	0.5–5	0.91 (ns)
Grontved, 2011	Television viewing	1655	8 (0.5%)	26,509	>25	8	1.13*
Hamer, 2008	Walking pace	4295	18 (0.4%)	147,063	20–93	11	0.68
Kodama, 2009	PF	10,679	33 (0.3%)	102,980	37–57	1–26	0.59
Nocon, 2008	PF/PA	1768	33 (1.9%)	883,372	na	4–20	0.59 (PF) 0.71 (PA)
Samitz, 2011	PA domains	6933	80 (1.2%)	844,026	56	11	0.65
Taylor, 2004	Exercise training (RCT)	>5000	48 (1%)	8940	55	1.5	0.80
Woodcock, 2010	PA	6210	22 (0.4%)	977,925	38–72	5–25	0.76

na: not available, ns: non-significant, PA: physical activity, PF: physical fitness, RR: relative risk of highest active group/lowest active or active/control, RCT: randomized controlled trials, *: RR per 2 hours of TV viewing per day.