

Methodology article

Decomposing the effects of physical activity and cardiorespiratory fitness on mortality

Julian Wolfson^{a,*}, Steven D. Stovitz^b, Steven N. Blair^c, Xuemei Sui^d, Duck-chul Lee^e, Ian Shrier^f^a University of Minnesota, School of Public Health, Division of Biostatistics, Minneapolis, USA^b University of Minnesota, Department of Family Medicine and Community Health, Minneapolis, USA^c Retired from University of South Carolina, Arnold School of Public Health, Departments of Exercise Science and Epidemiology and Biostatistics, Columbia, USA^d University of South Carolina, Department of Exercise Science, Division of Health Aspects of Physical Activity, Columbia, USA^e Iowa State University, College of Human Sciences, Department of Kinesiology, Ames, USA^f Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, Canada

ARTICLE INFO

Article history:

Received 16 April 2019

Received in revised form 6 September 2019

Accepted 6 September 2019

Available online 13 September 2019

Keywords:

Physical activity

Cardiorespiratory fitness

Diabetes

Hypertension

Mortality

Mediation

Interaction

Causal effects

ABSTRACT

Background: Characterizing the effects of physical activity (PA) and cardiorespiratory fitness (CRF) on mortality is challenging because the causal relationship between PA, CRF, and other cardiovascular risk factors is unclear.

Methods: To better understand the effects of PA and CRF on mortality, we re-analyzed data from 42,373 participants in the Aerobics Center Longitudinal Study (ACLS) using a modified version of VanderWeele's four-way causal effect decomposition method. The method was applied to decompose the causal effects of PA and CRF on median time to death into parts reflecting mediation, interaction, mediated interaction, and neither interaction nor mediation.

Results: We found that 67% of the effect of PA on mortality was mediated by CRF, while the effect of CRF was not significantly mediated by PA. The effects of both PA and CRF were mediated to a small extent by hypertension and diabetes. There were no meaningful interactions.

Conclusions: Our findings strengthen the evidence that the benefit on mortality from PA is largely mediated by its effect on CRF, and support efforts to increase longevity by encouraging PA.

© 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The Aerobics Center Longitudinal Study (ACLS) was a prospective observational study of men and women who were clinically examined at the Cooper Clinic in Dallas, TX to ascertain a number of baseline cardiovascular (CV) risk factors, including physical activity (PA) and cardiorespiratory fitness (CRF). In 2011, Lee et al. analyzed data from the ACLS to “define more clearly the benefits of PA and CRF to reduce mortality risk,” with the hope that the information “may be useful in developing future PA guidelines” [1]. The authors used Cox regression models to assess the effect of both PA and CRF on mortality, adjusted for age (years), year of baseline examination, body mass index (BMI, kg/m²), smoking status (never, former or current), presence or absence of hypertension, diabetes, hypercholesterolemia and parental cardiovascular disease (CVD) at baseline. In these models, CRF had a larger protective effect compared to PA. The risk ratio (RR, with 95% CI) for high vs low CRF was 0.56 (0.47 to 0.65) in

men, and 0.59 (0.40 to 0.85) in women, whereas the RR for recommended versus inactive PA was 0.87 (0.77 to 0.99) in men and 0.83 (0.59 to 1.15) for women. The authors concluded that “CRF was more strongly associated with all-cause mortality than PA.” [1] Based on the seminal work of Baron and Kenny [2], the study then assessed what the authors termed the “independent effects” of PA and CRF, defined as the effect of each variable adjusted for all the above variables and also adjusted for the other exposure variable, i.e., PA adjusted for CRF, and CRF adjusted for PA. In these models, the effect of CRF remained nearly the same in both men and women. However, the effect of PA was essentially eliminated in both men (RR = 1.05, 95% CI = 0.91 to 1.20) and women (RR = 0.95, 95% CI = 0.67 to 1.35). The authors concluded, “it is likely that the effect of PA on mortality is mediated largely by CRF.” [1]

While the data from Lee et al. [1] are consistent with their conclusions, they are also consistent with several other types of causal relationships, including interactions between variables and other mediation mechanisms. The relationship between PA and CRF is complex; one may mediate the other, but they may also interact to affect mortality. Most existing statistical methods assess either mediation or interaction (i.e., effect modification), but not both simultaneously, which could lead to interpretation of effect modification as mediation and vice

* Corresponding author at: A460 Mayo Building MMC 303, 420 Delaware St. SE, Minneapolis, MN 55455, USA.

E-mail address: juilanw@umn.edu (J. Wolfson).

versa. For example, Lee et al.'s results could also be explained if PA affects mortality differently in those who have high baseline CRF and those who have low baseline CRF, or if PA decreases the probability of diabetes (or hypertension or hypercholesterolemia) which, in turn, improves CRF.

In 2014, VanderWeele introduced a technique for decomposing the effects of exposure into four components reflecting mediation, interaction, both mediation and interaction, and neither mediation nor interaction [3]. While intuitively appealing, it has not been widely applied in analyzing real data. In this paper, we adapted the four-way decomposition method to reanalyze the data from the ACLS with the goal of characterizing the direct and indirect effects of PA and CRF on time to death. We present the results of this novel analysis, and discuss how the individual components of the decomposition can be interpreted in a cardiovascular risk management context.

Methods

Population

As described by Lee, et al. in 2011 [1], the ACLS was a prospective observational study of men and women who received preventive medical examinations during 1978–2002 at the Cooper Clinic in Dallas, TX. Among 50,244 participants aged 20–82 years at baseline, relatively healthy participants were included in this analysis (31,818 men and 10,555 women). The details of the participant demographics and measurements are outlined previously [1]. In brief, the participants were generally college graduates, non-Hispanic White, and middle to upper socioeconomic status. All participants underwent a standardized clinical evaluation by trained personnel including a medical history questionnaire and physical evaluation along with an exercise test, body composition assessments, blood pressure measurements, ECG, fasting blood chemistry analysis. There have been over 300 publications based on these data.

The main exposure variables for our analysis were PA and CRF. PA was assessed using a validated self-report questionnaire on leisure-time or recreational activities during the past 3 months [4]. The intensity of the activities were estimated via speed-specific or activity-

specific metabolic equivalent (MET) values from the Compendium of Physical Activities [5]. The MET value was then summed for all activities over a week to obtain MET-minutes/week of PA, which is the principal metric used in the 2008 PA Guidelines [6]. Participants were classified as either “inactive” (0 MET-minutes/week), “insufficient” (1–499 MET-minutes/week) or “recommended” (≥ 500 MET-minutes/week). CRF was defined as the total duration of a maximal treadmill test using a modified Balke protocol [7]. Details of the test have been published previously [4]. Participants were assigned to one of three fitness categories; low (least fit 20%), moderate (next fit 40%), or high (most fit 40%), based on cut-points derived from age- and sex-specific treadmill time distributions in the ACLS population, as published previously [8]. CRF was further dichotomized into “unfit” (low fitness) or “fit” (moderate or high fitness).

The main outcome of the study, and for our analysis, was all-cause mortality. Mortality follow-up was completed until the date of death for descendants or 31 December 2003 for survivors using the National Death Index. There were 1492 (469 per 10,000) and 230 (218 per 10,000) deaths in men and women, respectively.

Analysis

Our analyses were guided by two theoretical causal diagrams (Fig. 1a and b) reflecting competing hypotheses about the relationship between PA, CRF, and mortality. Fig. 1a reflects the hypothesis that CRF mediates the effect of PA on mortality, while Fig. 1b reflects the hypothesis that PA mediates the effect of CRF on mortality. Both figures include “upstream variables,” defined as those that could not have been the result of PA or CRF, i.e., sex, age, year of baseline measurement, smoking status, and parental CVD. We adjusted for these variables in our analyses. Since BMI could be affected by PA, and/or PA could affect BMI, we ran the primary analysis with and without BMI (under or normal weight: < 25 ; overweight: $BMI = 25–29.9$; obese: $BMI \geq 30$ kg/m^2) in the model and found that the results were similar. Hence, we chose to also include BMI in our models as an upstream variable. In addition to PA, CRF, mortality, and upstream variables, Fig. 1a and b also include “downstream” variables (denoted in gray) which could plausibly be

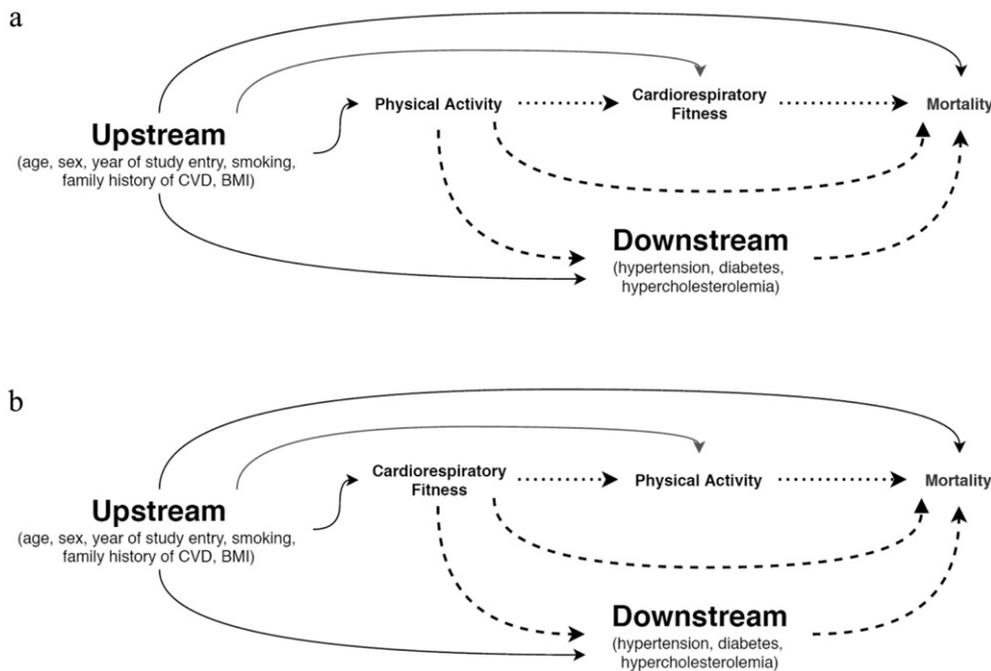


Fig. 1. a: Potential causal diagram on mortality with CRF serving as a mediator of PA. The causal relationships between upstream variables themselves is not displayed to improve clarity. All upstream variables need to be adjusted for unless one is willing to assume that 100% of the effect of one upstream variable was mediated by the other upstream variables. b: Potential causal diagram on mortality with PA serving as a mediator of CRF.

impacted by PA/CRF: presence of hypertension (HTN, systolic or diastolic blood pressure $\geq 140/90$ mmHg or history of hypertension), diabetes mellitus (DM, fasting glucose ≥ 126 mg/dL, current therapy with insulin or history of diabetes) and hypercholesterolemia (total cholesterol ≥ 240 mg/dL or history of hypercholesterolemia). These downstream variables represent alternate pathways through which the effects of PA and CRF on mortality could be mediated, and hence, as explained below, they may play an important role in estimating the causal effects of PA and CRF. The dotted arrows indicate paths mediated by CRF (Fig. 1a) and PA (Fig. 1b); dashed arrows indicate paths not mediated by PA and CRF.

To assess effect modification and mediation for PA and CRF, we adapted VanderWeele’s method which decomposes the effect of an exposure on an outcome into four main components: a Controlled Direct Effect (CDE), a Pure Indirect Effect (PIE), a Reference Interaction Effect (INT_{ref}) and a Mediated Interaction Effect (INT_{med}) [3]. The CDE quantifies the causal effect of exposure when the mediator is fixed at an arbitrary value, while the PIE quantifies the causal effect of the mediator when the exposure is fixed. The sum of the four components is the Total Effect (TE), and the components can be combined to estimate and make inference about the percent of the total effect of PA or CRF which is due to mediation ($\% \text{ mediated} = 100 \times [INT_{med} + PIE] / TE$) and to interaction ($\% \text{ interaction} = 100 \times [INT_{med} + INT_{ref}] / TE$). To extend the method to the right-censored time-to-death outcome in our application, we used parametric accelerated failure time (AFT) regression models. Unlike the semiparametric Cox proportional hazards models used by Lee et al. [1], which estimate the relative instantaneous hazard of death, AFT models estimate the relative median time to death. Also in contrast to Cox models, in AFT models protective exposures (e.g., higher CRF) are indicated by risk ratios >1 , corresponding to an increased median time to death. All analyses were performed in R [9]. Code for implementing the four-way decomposition is available at: [removed for blinding purposes].

Key to VanderWeele’s method is the estimation of the “direct” and “indirect” effects of exposure on outcome. Indirect effects are those which are mediated by another variable on the causal pathway between exposure and outcome, while direct effects are those which are not mediated by that variable. Note that indirect and direct effects are specific to an exposure-mediator pair; it is possible (indeed, likely) that the “direct” effect of exposure which bypasses a given mediator is in fact mediated by other variables in the system. We therefore

estimated mediation and interaction effects of each exposure-mediator pair by omitting primary and downstream variables other than that pair from the analysis. For example, to assess whether hypertension mediates the effect of PA on mortality, we omitted CRF, diabetes, and hypercholesterolemia from the model. Then, the indirect effect captures the effect of PA on mortality acting via hypertension, and the direct effect reflects a combination of all the other paths from PA to mortality (including via CRF, diabetes, hypercholesterolemia, and any other omitted variables).

This approach is valid if Fig. 1a and b accurately reflect the causal relationships between the primary, upstream, and downstream variables and mortality. However, these figures do not reflect the possibility that the downstream variables could be associated with the mediator. As described in existing literature [10], the presence of variables affected by exposure is potentially problematic if they are confounders of the relationship between the mediator and mortality; in this case, they lie on both the direct path (since they are affected by exposure, but omitted) and indirect path (since they are associated with the mediator) from exposure to outcome. Therefore, they must convey information about different exposure settings simultaneously, a phenomenon which has been termed the “recanting witness problem” [10]. When the recanting witness problem occurs, the components of the four-way decomposition cannot be validly estimated from data without additional assumptions. This issue is addressed at greater length in the Discussion.

Results

Table 1 shows the decomposition of the effects of PA and CRF on mortality into mediated and interaction effects. After adjusting for all upstream variables, recommended PA (vs. insufficient/inactive) was associated with a 9% (95% CI: 3%, 15%) increase in median time to death compared with individuals in the insufficient or inactive category. Decomposition analysis found that 67% (95% CI: 27%, 388%) of the effect of PA was mediated by CRF, and a small percentage of the effect of PA was mediated by HTN (5%, 95% CI: 2%, 18%) and Diabetes (3%, 95% CI: 1%, 10%). There was no statistically significant interaction between PA and CRF, HTN, DM, or hypercholesterolemia. Regarding CRF, those who were “fit” (vs unfit) had a 33% increase in the median time to death (95% CI: 25%, 41%). A small amount of the effect of CRF was mediated by HTN (7%, 95% CI: 5%, 10%) and DM (4%, 95% CI: 1%, 7%). There

Table 1
Adjusted, mediated and interaction effects of PA and CRF on mortality.

Exposure	Mediator/ interacting variable	Adjusted effect of exposure ^a	% Mediated	% Interaction
Physical activity (Recommended vs. Insufficient/Inactive)	(None)	1.09 (1.03 to 1.15)	N/A	N/A
	Cardiorespiratory Fitness	1.02 (0.96, 1.08)	67% (27%, 388%)	-14% (-1103%, 195%)
	Hypertension	1.08 (1.02, 1.14)	5% (2%, 18%)	14% (-24%, 72%)
	Diabetes	1.08 (1.03, 1.15)	3% (1%, 10%)	1% (-13%, 22%)
	Hypercholesterolemia	1.09 (1.03, 1.15)	1% (-2%, 6%)	4% (-31%, 77%)
Cardiorespiratory fitness (Fit vs. Unfit)	(None)	1.33 (1.25 to 1.41)	N/A	N/A
	Physical Activity	1.32 (1.24, 1.40)	2% (-8%, 9%)	-2% (-30%, 20%)
	Hypertension	1.30 (1.22, 1.38)	7% (5%, 10%)	2% (-7%, 11%)
	Diabetes	1.31 (1.23, 1.39)	4% (1%, 7%)	1% (-1%, 3%)
	Hypercholesterolemia	1.32 (1.25, 1.41)	1% (-0%, 2%)	-1% (-11%, 7%)

All analyses are adjusted for age, sex, year of study entry, smoking, family history of CVD, and BMI.

^a Expressed as ratio of median time to death for high vs. low level of exposure (Recommended vs. Insufficient/Inactive for PA, Fit vs. Unfit for CRF). Estimated from an accelerated failure time regression model for time to death.

was no statistically significant interaction between CRF and PA, HTN, DM, or hypercholesterolemia. Fig. S1 in the Supplementary Materials provides estimates of the total effects of PA and CRF along with the components of the four-way decomposition.

In the Supplementary Materials, Table S1 summarizes a sensitivity analysis wherein the four-way decomposition analyses from Table 1 are repeated, but with other potential mediators included as confounders instead of omitted. The estimated % mediation and % interaction are very similar to the original results, but with substantially wider confidence intervals. Table S2 reinforces the findings in Table S1 by showing the % mediation and % interaction for HTN, DM, and hypercholesterolemia viewed as exposures. The only % mediation values that are statistically significant are small in magnitude (<10%), suggesting that the pathways carrying the indirect effects of PA and CRF include only a single mediator. In Tables 1, S1, and S2, some of the % Mediated and % Interaction estimates have very wide confidence intervals with endpoints beyond $\pm 100\%$, due to the fact that these quantities represent ratios of estimates that can vary substantially when the total effect of exposure is small.

Discussion

Our study reanalyzed data from the Aerobics Center Longitudinal Study to quantify the contributions of mediation and interaction in explaining the effects of PA and CRF on mortality. The results of our re-analysis were qualitatively consistent with the findings of Lee et al. [1] We found that PA had a much smaller effect than CRF on mortality: those who were physically active had a 9% higher median time to death than those who were insufficiently active or inactive, while those who were fit had a 33% higher median time to death as compared with those who were unfit. Using the four-way causal effect decomposition method of VanderWeele [3], we found that approximately two-thirds of PA's effect on mortality was mediated by its effect on improving CRF. In contrast, PA was not a meaningful mediator of the effect of CRF on mortality. We also found that a small proportion of the benefit of PA was via mediated effects through decreasing HTN and DM. Similarly, a small proportion of the benefit of higher CRF was via decreasing hypertension, DM and hypercholesterolemia. We found no statistically significant interactions with any of the main covariates on the effects of PA or CRF.

While qualitatively similar, our results bring additional insight to those reported in Lee et al. [1] by providing evidence for or against particular mechanisms of action for PA and CRF that cannot be distinguished using the traditional Baron and Kenny [2] approach to assess mediation. Our findings are consistent with the causal diagram in Fig. 1a, and inconsistent with Fig. 1b as well as other alternative causal mechanisms. For example, our results argue against the hypothesis that PA's effect on CRF is itself mediated via DM (or HTN or hypercholesterolemia), since only a small fraction of the effect of PA on mortality was mediated by DM/HTN/hypercholesterolemia whereas 67% was mediated by CRF. Further, our analyses suggest little interaction between CRF or PA and these other variables. In estimating the separate mediating effect of each variable of interest, we excluded other potential mediators from our statistical models, but this omission could be problematic if the omitted variables confound the mediator-outcome relationship. However, sensitivity analyses showed that including potential mediators as confounders had a minimal impact on the results.

Beyond the usual ignorability ("no unmeasured confounders") assumption, our analysis relies on the assumption that no confounders of the mediator-outcome relationships are themselves affected by exposure (i.e., no "recanting witnesses") [10]. Fig. 1a and b omit arrows connecting the mediators, including CRF (in 1a), PA (in 1b), hypertension, diabetes, and hypercholesterolemia. Fig. S2a and b show diagrams representing these scenarios, for example where hypertension is affected by PA and affects both CRF and mortality. While this is certainly

a theoretical concern since direct and indirect effects are not well-defined when there are recanting witness variables, in our data the indirect effects of PA via hypertension, diabetes, and hypercholesterolemia are relatively modest, suggesting that these three variables are not highly influential recanting witnesses for the relationship between PA and mortality. Similarly, the indirect effects of CRF are negligible via all candidate mediators, hence it is unlikely that PA acts as an influential recanting witness for the relationship between CRF and mortality. One approach that avoids the recanting witness problem is to estimate slightly different causal quantities called the randomized intervention estimates [11]. However, the randomized intervention analogues of CDE, PIE, INT_{ref} and INT_{med} are difficult to interpret in a clinical context since they require imagining that each individual can be assigned any value of the mediator chosen at random from its conditional distribution given exposure. Further, the randomized intervention interpretation is valid only if the exposure and recanting witness do not interact to affect the mediator, an assumption which may be implausible.

Vanderweele's four-way decomposition involves the Controlled Direct Effect (CDE) and Pure Indirect Effect (PIE), which differ from the so-called "natural" direct and indirect effects that others have argued are more clinically interpretable [12] but do not distinguish effects of mediation and interaction. While we display the estimates of CDE, PIE, INT_{ref} and INT_{med} to allow different combinations and therefore calculation of these effects [reference: unification paper], the primary conclusions from our data analysis are based combinations that on the % mediated and % interaction, quantities that combine components of the four-way decomposition to yield more interpretable quantities. For example, % mediated is based on $PIE + INT_{med}$ which equals the Total Indirect Effect, a type of natural effect. While % mediated and % interaction could be estimated from separate models involving simpler decompositions, one advantage of applying the four-way decomposition method is that it provides a unified framework for estimation and inference on both quantities simultaneously.

Our re-analysis was limited by the fact that PA, CRF, other potential mediators and covariates were only assessed at baseline, and could be subject to measurement error. Any changes made after the initial assessment (for example, someone who was inactive at baseline and then became active later) were not captured; had longitudinal measurements of these variables been available, our analysis would have to be modified to account for time-varying confounding [13], but we are not aware of any existing techniques to do this. The measurement of PA was via self-report rather than with objective monitors that have become more prevalent since these data were gathered. Self-reported PA undoubtedly has errors, with many people over-reporting their amounts of activity [14]. Also, the measurement of PA focused on leisure-time PA and did not include assessment of PA at home, during work or via active commuting. Since the population of the study was disproportionately in executive or other advanced professional positions (another limitation when applying our results to the general population), leisure-time PA likely made up the majority of daily PA. Finally, CRF was assessed via time on a treadmill rather than direct VO_{2max} testing. Treadmill time may be affected by issues such as age, gender, body weight, medical condition, and motivation. Due to the nature of the decomposition approach, continuous-valued exposures and mediator variables were dichotomized, and the results could change if different dichotomization thresholds were used.

One interpretation of our findings is that since PA has a smaller total effect than CRF, and since PA's effect is strongly mediated by CRF, then PA is of lesser importance than CRF. However, the key question for a patient is "what can I do to live a longer life?" Thus, the important question may not be which has the largest total effect (approximately 25–50% of CRF seems to be due to genetic makeup) [15], nor which has the largest independent effect. Rather the important question may

be, what can or cannot be modified and by what means? Since PA is certainly modifiable and increasing PA the best way for a person to modify CRF given their genetic makeup, our findings support efforts to design and implement interventions that increase PA.

Funding sources

The current study re-analyzing previously published data was not supported by any funding.

The collection of the original data and analyses for the previously published paper (Lee et al. 2011) was funded by the National Institutes of Health grants AG06945 and HL62508, an unrestricted research grant from the Coca-Cola Company, the Korea NEST Foundation for the Next Generation Sports Talent, Spanish Ministry of Education (EX-2008-0641) and European Community Sixth RTD Framework Programme (Contract FOOD-CT-2005-007034).

Declaration of interest

The authors declare no conflicts of interest

Acknowledgments

The authors thank the Cooper Clinic physicians and technicians for collecting the baseline data, and staff at the Cooper Institute for data entry and data management.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gloepi.2019.100009>.

References

- [1] Lee D-CC, Sui X, Ortega FB, et al. Comparisons of leisure-time physical activity and cardiorespiratory fitness as predictors of all-cause mortality in men and women. *Br J Sports Med* 2011;45(6):504–10. <https://doi.org/10.1136/bjism.2009.066209> (pii).
- [2] Baron RM, Kenny DA. *Kenny*, 1986. *J Pers Soc Psychol* 1986;51:1173–82.
- [3] VanderWeele TJ. A unification of mediation and interaction: a 4-way decomposition. *Epidemiology* 2014;25(5). <https://doi.org/10.1097/EDE.0000000000000121>.
- [4] Blair SN, Kannel WB, Kohl HW, Goodyear N, Wilson PW. Surrogate measures of physical activity and physical fitness. Evidence for sedentary traits of resting tachycardia, obesity, and low vital capacity. *Am J Epidemiol* 1989;129(6):1145–56.
- [5] Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000;32(9):S498–504 Suppl.
- [6] Physical Activity Guidelines Advisory Committee report, 2008. To the Secretary of Health and Human Services. Part a: executive summary. *Nutr Rev* 2009;67(2):114–20. <https://doi.org/10.1111/j.1753-4887.2008.00136.x>.
- [7] Balke B, Ware RW. An experimental study of physical fitness of air force personnel. *U S Armed Forces Med J* 1959;10(May):675–88.
- [8] Sui X, LaMonte MJ, Blair SN. Cardiorespiratory fitness and risk of nonfatal cardiovascular disease in women and men with hypertension. *Am J Hypertens* 2007;20(6):608–15. <https://doi.org/10.1016/j.amjhyper.2007.01.009>.
- [9] Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: R package for causal mediation analysis. *J Stat Softw* 2014;59(5). <http://www.jstatsoft.org/v59/i05/>.
- [10] Tchetgen Tchetgen EJ, VanderWeele TJ. Identification of natural direct effects when a confounder of the mediator is directly affected by exposure. *Epidemiology* 2014;25(2):282–91. <https://doi.org/10.1097/EDE.0000000000000540>.
- [11] VanderWeele T. *Explanation in causal inference: Methods for mediation and interaction*. New York: Oxford University Press; 2015.
- [12] Vanderweele TJ, Vansteelandt S. Conceptual issues concerning mediation, interventions and composition. *Stat Interface* 2009;2(4):457–68. <https://doi.org/10.4310/SII.2009.v2.n4.a7>.
- [13] Mansournia MA, Etminan M, Danaei G, Kaufman JS, Collins G. Handling time varying confounding in observational research. *BMJ* 2017;359:j4587. <https://doi.org/10.1136/bmj.j4587>.
- [14] Adams SA, Matthews CE, Ebbeling CB, et al. The effect of social desirability and social approval on self-reports of physical activity. *Am J Epidemiol* 2005;161(4):389–98. <https://doi.org/10.1093/aje/kwi054>.
- [15] Bouchard C. Genomic predictors of trainability. *Exp Physiol* 2012;97(3):347–52. <https://doi.org/10.1113/expphysiol.2011.058735>.