ESC European Society of Cardiology

European Journal of Preventive Cardiology (2023) **30**, 230–231
https://doi.org/10.1093/eurjpc/zwac288

**INVITED EDITORIAL**

# Maximizing the effects of physical activity on cardiovascular health: a matter of time?

**Juliana Alexandra Hernández Vargas, Silvia Juliana Trujillo-Cáceres, Julieth Pilar Uriza-Pinzón, and Oscar H. Franco***

Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Huispost nr. STR 6.131, 3508 GA Utrecht, Netherlands

*Online publish-ahead-of-print 7 December 2022*

**This editorial refers to 'Setting your clock: associations between timing of objective physical activity and cardiovascular disease risk in the general population', by G. Albalak *et al.*, https://doi.org/10.1093/eurjpc/zwac239.**

Cardiovascular diseases (CVDs) remain the leading cause of death and disability worldwide. Between 1990 and 2019, the number of CVD deaths increased by 54%.[1] CVD burden is mainly attributed to modifiable and metabolic risk factors including a sedentary lifestyle.[1]

Annually, ~3.9 million premature deaths globally could be preventable with adequate physical activity (PA).[2] For decades, the effect of PA on CVD has been studied with consistent results associating an active lifestyle with lower risks of CVD and mortality, and improvements in quality of life and healthy ageing.[3] Therefore, PA is a cornerstone in cardiovascular prevention as addressed in current guidelines. Most recommendations focus on frequency, intensity, and duration and rarely address the timing of exercise or '*chronoactivity*'.[4]

Chronoactivity adds a new dimension to the study of the known effects of PA on CVD, since exercise may act as a potential cue (zeitgeber), favouring the circadian system homeostasis.[5] The expression of cardiometabolic, inflammatory and genetic markers related to cardiovascular risk factors vary during the day, thus peaks of PA at different times of the day may have a differential effect on cardiovascular health to be considered in the future for tailoring PA.

Current evidence comes from clinical trials[6] and observational data in specific target groups (women, obese, and persons with diabetes or hypertension)[6–11] or the general population.[12] Most of these studies have focused on cardiometabolic risk factors[6–10,12,13] rather than the incidence of CVD, mainly using non-prospective approaches.

Overall, some studies suggest that morning exercise may have protective effects on cardiometabolic functioning compared to evening PA,[7–9,13] while others have found opposite results.[6,10–12] A high heterogeneity regarding the study designs, the population included, the definition of PA and outcomes of interest, as well as the sample size (smaller in clinical trials) and bias control, especially confounding, may partially explain the lack of consistency.

Moreover, certain studies have hypothesized that time-dependent effects of PA may only result from high-intensity activity, but could they be independently associated (irrespective of intensity) with the risk of CVD in a general population?

Interested in addressing the above, Albalak *et al.*[14] published their study in this issue of the European Journal of Preventive Cardiology prospectively evaluating the association between different PA timing patterns and CVD risk in a large general population from the UK Biobank study. Furthermore, the authors investigated if this relation was modified by sex, total PA, and sleep chronotype. CVD was defined as coronary artery disease (CAD) or stroke. Physical activity was objectively measured over seven days with an accelerometer and then grouped into clusters of PA timing.

In brief, the authors described four intraday chronoactivity patterns among 86 657 participants: (i) an average (midday) type, used as a reference in all models; (ii) an early morning peak; (iii) a late morning peak; and (iv) evening peak. Overall, when comparing with the reference group, people with late morning PA had a lower risk of CAD, any stroke, and ischaemic stroke (16%, 17%, and 21% lower, respectively). The risk reduction was higher in women but was not modified by total activity level and chronotype. The main finding is that timing of PA is an independent factor associated with differential CVD risk in the general population, supporting a novel approach in research and clinical prescription of PA to reduce the burden of CVD in our ageing populations, which should take into account the timing of activity.

These results align with the current evidence supporting the protective effect of morning PA on cardiovascular outcomes while adding a prospective approach. Multiple methodological strengths are worth mentioning, starting with the broad general population-based UK Biobank cohort with ongoing longitudinal follow-up. Also, the objective assessment of PA, the use of clustering methods to classify chronoactivity patterns, and investigation of the chronotype.

Nonetheless, as the authors discussed, research on behavioural factors must overcome some challenges. Dealing with time-varying exposures, improving the PA definition's accuracy and feasibility through follow-up, limiting residual confusion, and considering the role of mediators are among the most relevant.

Regarding the first concern, most health variables, especially behaviours, are not static during life.[15] This study measured exposure and covariates at a single point during the follow-up, not allowing the possibility to determine time-varying effects. The evaluation of trajectories of PA

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Preventive Cardiology* or of the European Society of Cardiology.

* Corresponding author. Tel: +31 6 50177549, Email: o.h.franco@umcutrecht.nl

has consistently described a dose-response gradient with sustainable cardiometabolic benefits in people with a constant level of activity during life or even those becoming active after a period of sedentarism,[15] thus a new challenge would be to explore the role of chronoactivity in the relation between trajectories of activity and cardiovascular health.

In addition, to address the second point, future studies should improve the definition of PA by combining objective and self-reported measurements, which would also help to obtain more measurements over time.

Since the main findings come from the model adjusted for sex and age, residual confounding may still be present. Variables such as BMI, smoking, diet, education, socioeconomic status, and some comorbidities increase the risk of CVD and the probability to exercise, so they could also modify intraday patterns of PA. Moreover, future research should jointly evaluate chronotype, chrononutrition, and the role of timing of other lifestyle risk factors[5] to fully assess whether synchronizing lifestyle timing with the biological clock increases the benefits of exercise in cardiovascular health.

In closing, this study suggests that time-oriented PA independently lowers the risk of CVD in the general population and highlights the importance of extending research on chronoactivity. However, controversy remains about the best time to exercise. Further studies as large randomized controlled trials including repeated measures of the exposure and covariates and considering the role of the circadian cycle are needed. Knowing the best time to do PA is still under research; in the meantime, the best formula is to continue exercising. Regardless of the clock, keep moving!

## Funding

None declared.

**Conflict of interest:** The authors declare no conflicts of interest regarding the research, authorship, or publication of this article.

## References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, *et al.* Global burden of cardiovascular diseases and risk factors, 1990–2019. *J Am Coll Cardiol* 2020;**76**:2982–3021.
2. Strain T, Brage S, Sharp SJ, Richards J, Tainio M, Ding D, *et al.* Use of the prevented fraction for the population to determine deaths averted by existing prevalence of physical activity: a descriptive study. *Lancet Glob Health* 2020;**8**:e920–e930.
3. Wahid A, Manek N, Nichols M, Kelly P, Foster C, Webster P, *et al.* Quantifying the association between physical activity and cardiovascular disease and diabetes: a systematic review and meta-analysis. *J Am Heart Assoc* 2016;**5**:e002495.
4. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, *et al.* 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2022;**42**:3227–3337.
5. Sempere-Rubio N, Aguas M, Faubel R. Association between chronotype, physical activity and sedentary behaviour: a systematic review. *Int J Environ Res Public Health* 2022;**19**:9646.
6. Liu H, Liu S, Wang K, Zhang T, Yin L, Liang J, *et al.* Time-dependent effects of physical activity on cardiovascular risk factors in adults: a systematic review. *Int J Environ Res Public Health* 2022;**19**:14194.
7. Schumacher LM, Thomas JG, Raynor HA, Rhodes RE, Bond DS. Consistent morning exercise may be beneficial for individuals with obesity. *Exerc Sport Sci Rev* 2020;**48**:201–208.
8. Chomistek AK, Shiroma EJ, Lee IM. The relationship between time of day of physical activity and obesity in older women. *J Phys Act Health* 2016;**13**:416–418.
9. Albalak G, Stijntjes M, Wijsman CA, Slagboom PE, van der Ouderaa FJ, Mooijaart SP, *et al.* Timing of objectively-collected physical activity in relation to body weight and metabolic health in sedentary older people: a cross-sectional and prospective analysis. *Int J Obes* 2022;**46**:515–522.
10. Brito LC, Peçanha T, Fecchio RY, Pio-Abreu A, Silva G, Mion-Junior D, *et al.* Comparison of morning versus evening aerobic-exercise training on heart rate recovery in treated hypertensive men: a randomized controlled trial. *Blood Press Monit* 2021; **26**:388–392.
11. Qian J, Walkup MP, Chen SH, Brubaker PH, Bond DS, Richey PA, *et al.* Association of objectively measured timing of physical activity bouts with cardiovascular health in type 2 diabetes. *Diabetes Care* 2021;**44**:1046–1054.
12. van der Velde JHPM, Boone SC, Winters-van Eekelen E, Hesselink MKC, Schrauwen-Hinderling VB, Schrauwen P, *et al.* Timing of physical activity in relation to liver fat content and insulin resistance. *Diabetologia* 2022. https://doi.org/10.1007/s00125-022-05813-3.
13. Park S, Jastremski CA, Wallace JP. Time of day for exercise on blood pressure reduction in dipping and nondipping hypertension. *J Hum Hypertens* 2005;**19**:597–605.
14. Albalak G, Stijntjes M, van Bodegom D, Jukema JW, Atsma DE, van Heemst D, *et al.* Setting your clock: associations between timing of objective physical activity and cardiovascular disease risk in the general population. *Eur J Prev Cardiol* 2023;**30**:232–240.
15. Gonzalez-Jaramillo N, Wilhelm M, Arango-Rivas AM, Gonzalez-Jaramillo V, Mesa-Vieira C, Minder B, *et al.* Systematic review of physical activity trajectories and mortality in patients with coronary artery disease. *J Am Coll Cardiol* 2022;**79**:1690–1700.