

1 **In lifestyle and prevention, the whole is surely greater than the sum of its parts**

2 Nathalia Gonzalez-Jaramillo ^{1,2}

3 Arjola Bano ^{1,2}

4 Oscar H. Franco ¹

5 ¹ Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland.

6 ² Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern,
7 Switzerland.

8 **Funding:** The authors received no financial support for the research, authorship, and/or
9 publication of this article.

10 **Declaration of conflicting interests:** The authors declared no potential conflicts of interest
11 concerning the research, authorship, and/or publication of this article.

12 **Address all correspondence and requests for reprints to:**

13 Oscar H. Franco

14 Institute of Social and Preventive Medicine, University of Bern

15 Office 376

16 Mittelstrasse 43

17 3012 Bern Switzerland

18 Tel: +41 31 631 33 50

19 E-mail: oscar.franco@ispm.unibe.ch

20
21 **Keywords:** physical activity, coronary heart disease, prevention.

1 More than 17 million people die from cardiovascular disease (CVD) each year.¹ A significant
2 proportion of these deaths could be prevented through an adequate control of risk factors that are
3 primarily associated with lifestyle. Physical inactivity, obesity, poor diet, smoking, total
4 cholesterol, hypertension, and diabetes are recognized as key modifiable cardiovascular risk
5 factors.² As a result, tailored interventions aimed to change lifestyle behaviours based on
6 individual risk estimation are a core component of guidelines on CVD prevention.³ Despite this,
7 individual counselling targeting a specific risk is often difficult as inter-relations of established
8 risk factors for coronary heart disease are complex and intertwined.

9 Physical inactivity is an important contributor to premature mortality, morbidity, and disability-
10 adjusted life years for adults in most of the world.⁴ Evidence from basic science and clinical
11 research has shown that physical inactivity increases the generation of vascular reactive oxygen
12 species which in turn leads to endothelial dysfunction and atherosclerosis.⁵ Likewise, diabetes,
13 hypercholesterolemia, hypertension, and smoking are associated with chronic inflammation⁶ and
14 increased oxidative stress, contributing to atherosclerosis.⁷ Therefore, a comprehensive
15 assessment of the individual contribution of physical activity (PA) to CVD risk in the presence
16 or absence of other risk and mediator factors may help guide prognosis and tailored prescription
17 of PA to prevent CVD in the general population.

18 In this issue of the European Journal of Preventive Cardiology, Fortuin-de Smidt et al.
19 investigated the contribution of PA to the prevention of coronary heart disease (CHD) in a broad
20 European population from the EPIC cohort with a variable presence of CVD risk factors.⁸
21 Among 23,576 participants, the authors evaluated CHD risk across several combinations of
22 cardiovascular risk factors with four baseline PA nominal categories as measured by the
23 Cambridge physical activity index. Compared with the reference category of combined physical

1 inactivity without CVD risk factors, the study found that in the absence of risk factors even small
2 amounts of PA were protective against CHD. However, in the presence of obesity,
3 hypercholesterolemia, hypertension, diabetes, or current smoking, PA decreased but did not
4 completely attenuate the excess in CHD risk conferred by the above-mentioned risk factors. For
5 instance, inactive patients who smoked had 2.5 times higher CHD risk than inactive participants
6 who never smoked, whereas moderately active participants who smoked still had a 2.1 times
7 increased CHD risk. Similarly, inactive patients with diabetes had a 2.4 higher CHD risk than
8 inactive participants without diabetes, whereas moderately active participants with diabetes had 2
9 times increased CHD risk. The results were consistent across the various models, further
10 supporting the estimated contribution of a physically active lifestyle. Noteworthy, the authors
11 reported that if a causal effect of PA is assumed, 5% of CHD events in the study population
12 could be prevented by moving from the inactive to the active category in the presence of the
13 analyzed CVD risk factors. Nevertheless, PA levels and CVD risk factors were only measured at
14 baseline, and it was not evaluated whether participants remained in the same risk status and PA
15 category during follow-up.

16 PA behaviours may vary during the life course.⁹ The association of CHD risk with baseline risk
17 profile and PA levels does not account for within-person variation over the long term, potentially
18 diluting the protective effects of activity. As shown by a recent study on PA trajectories among
19 patients with established CHD, continuing an active lifestyle over the years is associated with the
20 greatest longevity.¹⁰ However, patients with heart disease can overcome prior years of inactivity
21 and obtain survival benefits by taking up exercise later in life. By contrast, the benefits of PA can
22 be weakened or even lost if the activity is not maintained.¹⁰

1 In addition to PA trajectories, other cardiovascular risk factors which were also evaluated only at
2 baseline can change over follow-up. This may need to also be taken into account in future
3 investigations. Therefore, a key theme for further research should be to jointly analyze not only
4 the levels and contributions but also the interactions and trajectories of PA and other healthy
5 behaviours throughout the life course. Finally, the combined use of more objective (e.g.,
6 accelerometers) and subjective (e.g., validated questionnaires) PA measures could increase PA
7 assessments' accuracy over time. This may allow for determining reliable estimates of PA
8 changes and evaluate the effectiveness of interventions to improve PA across the spectrum of
9 heart disease risk.

10 In conclusion, the currently available evidence on CHD prevention indicates that tailored
11 recommendations require a complete risk profile evaluation and should target physical inactivity,
12 obesity, diet, smoking, total cholesterol, hypertension, and diabetes. In lifestyle and prevention,
13 the whole is surely greater than the sum of its parts.

14

15

1 References

- 2 1. Naghavi M, Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, Aboyans V, Adetokunboh
3 O, Afshin A, Agrawal A, Ahmadi A, Ahmed MB, Aichour AN, Aichour MTE, Aichour I, Aiyar S, Alahdab F,
4 Al-Aly Z, Alam K, Alam N, Alam T, Alene KA, Al-Eyadhy A, Ali SD, Alizadeh-Navaei R, Alkaabi JM, Alkerwi
5 Aa, Alla F, Allebeck P, Allen C, Al-Raddadi R, Alsharif U, Altirkawi KA, Alvis-Guzman N, Amare AT, Amini E,
6 Ammar W, Amoako YA, Anber N, Andersen HH, Andrei CL, Androudi S, Ansari H, Antonio CAT, Anwari P,
7 Ärnlöv J, Arora M, Artaman A, Aryal KK, Asayesh H, Asgedom SW, Atey TM, Avila-Burgos L, Avokpaho
8 EFG, Awasthi A, Babalola TK, Bacha U, Balakrishnan K, Barac A, Barboza MA, Barker-Collo SL, Barquera S,
9 Barregard L, Barrero LH, Baune BT, Bedi N, Beghi E, Béjot Y, Bekele BB, Bell ML, Bennett JR, Bensenor IM,
10 Berhane A, Bernabé E, Betsu BD, Beuran M, Bhatt S, Biadgilign S, Bienhoff K, Bikbov B, Bisanzio D,
11 Bourne RRA, Breitborde NJK, Bulto LNB, Bumgarner BR, Butt ZA, Cahuana-Hurtado L, Cameron E,
12 Campuzano JC, Car J, Cárdenas R, Carrero JJ, Carter A, Casey DC, Castañeda-Orjuela CA, Catalá-López F,
13 Charlson FJ, Chibueze CE, Chimed-Ochir O, Chisumpa VH, Chittheer AA, Christopher DJ, Ciobanu LG,
14 Cirillo M, Cohen AJ, Colombara D, Cooper C, Cowie BC, Criqui MH, Dandona L, Dandona R, Dargan PI, das
15 Neves J, Davitoiu DV, Davletov K, de Courten B, Defo BK, Degenhardt L, Deiparine S, Deribe K, Deribew
16 A, Dey S, Dicker D, Ding EL, Djalalinia S, Do HP, Doku DT, Douwes-Schultz D, Driscoll TR, Dubey M,
17 Duncan BB, Echko M, El-Khatib ZZ, Ellingsen CL, Enayati A, Ermakov SP, Erskine HE, Eskandarieh S,
18 Esteghamati A, Estep K, Farinha CSeS, Faro A, Farzadfar F, Feigin VL, Fereshtehnejad S-M, Fernandes JC,
19 Ferrari AJ, Feyissa TR, Filip J, Finegold S, Fischer F, Fitzmaurice C, Flaxman AD, Foigt N, Frank T, Fraser M,
20 Fullman N, Fürst T, Furtado JM, Gakidou E, Garcia-Basteiro AL, Gebre T, Gebregergs GB, Gebrehiwot TT,
21 Gebremichael DY, Geleijnse JM, Genova-Maleras R, Gesesew HA, Gething PW, Gillum RF, Giref AZ,
22 Giroud M, Giussani G, Godwin WW, Gold AL, Goldberg EM, Gona PN, Gopalani SV, Gouda HN, Goulart
23 AC, Griswold M, Gupta R, Gupta T, Gupta V, Gupta PC, Haagsma JA, Hafezi-Nejad N, Hailu AD, Hailu GB,
24 Hamadeh RR, Hambisa MT, Hamidi S, Hammami M, Hancock J, Handal AJ, Hankey GJ, Hao Y, Harb HL,
25 Hareri HA, Hassanvand MS, Havmoeller R, Hay SI, He F, Hedayati MT, Henry NJ, Heredia-Pi IB, Herteliu C,
26 Hoek HW, Horino M, Horita N, Hosgood HD, Hostiuc S, Hotez PJ, Hoy DG, Huynh C, Iburg KM, Ikeda C,
27 Ileanu BV, Irenso AA, Irvine CMS, Islam SMS, Jacobsen KH, Jahanmehr N, Jakovljevic MB, Javanbakht M,
28 Jayaraman SP, Jeemon P, Jha V, John D, Johnson CO, Johnson SC, Jonas JB, Jürisson M, Kabir Z, Kadel R,
29 Kahsay A, Kamal R, Karch A, Karimi SM, Karimkhani C, Kasaeian A, Kassaw NA, Kassebaum NJ, Katikireddi
30 SV, Kawakami N, Keiyoro PN, Kemmer L, Kesavachandran CN, Khader YS, Khan EA, Khang Y-H, Khoja ATA,
31 Khosravi MH, Khosravi A, Khubchandani J, Kiadaliri AA, Kielling C, Kivlan D, Kim YJ, Kim D, Kimokoti RW,

1 Kinfu Y, Kissoon N, Kivimaki M, Knudsen AK, Kopec JA, Kosen S, Koul PA, Koyanagi A, Kulikoff XR, Kumar
2 GA, Kumar P, Kutz M, Kyu HH, Lal DK, Laloo R, Lambert TLN, Lan Q, Lansingh VC, Larsson A, Lee PH,
3 Leigh J, Leung J, Levi M, Li Y, Li Kappe D, Liang X, Liben ML, Lim SS, Liu PY, Liu A, Liu Y, Lodha R,
4 Logroscino G, Lorkowski S, Lotufo PA, Lozano R, Lucas TCD, Ma S, Macarayan ERK, Maddison ER, Magdy
5 Abd El Razek M, Majdan M, Majdzadeh R, Majeed A, Malekzadeh R, Malhotra R, Malta DC, Manguerra
6 H, Manyazewal T, Mapoma CC, Marczak LB, Markos D, Martinez-Raga J, Martins-Melo FR, Martopullo I,
7 McAlinden C, McGaughey M, McGrath JJ, Mehata S, Meier T, Meles KG, Memiah P, Memish ZA,
8 Mengesha MM, Mengistu DT, Menota BG, Mensah GA, Meretoja TJ, Meretoja A, Millea A, Miller TR,
9 Minnig S, Mirarefin M, Mirrakhimov EM, Misganaw A, Mishra SR, Mohamed IA, Mohammad KA,
10 Mohammadi A, Mohammed S, Mokdad AH, Mola GLD, Mollenkopf SK, Molokhia M, Monasta L,
11 Montañez JC, Montico M, Mooney MD, Moradi-Lakeh M, Moraga P, Morawska L, Morozoff C, Morrison
12 SD, Mountjoy-Venning C, Mruts KB, Muller K, Murthy GVS, Musa KI, Nachega JB, Naheed A, Naldi L,
13 Nangia V, Nascimento BR, Nasher JT, Natarajan G, Negoi I, Ngunjiri JW, Nguyen CT, Nguyen QL, Nguyen
14 TH, Nguyen G, Nguyen M, Nichols E, Ningrum DNA, Nong VM, Noubiap JJN, Ogbo FA, Oh I-H, Okoro A,
15 Olagunju AT, Olsen HE, Olusanya BO, Olusanya JO, Ong K, Opio JN, Oren E, Ortiz A, Osman M, Ota E, Pa
16 M, Pacella RE, Pakhale S, Pana A, Panda BK, Panda-Jonas S, Papachristou C, Park E-K, Patten SB, Patton
17 GC, Paudel D, Paulson K, Pereira DM, Perez-Ruiz F, Perico N, Pervaiz A, Petzold M, Phillips MR, Pigott
18 DM, Pinho C, Plass D, Pletcher MA, Polinder S, Postma MJ, Pourmalek F, Purcell C, Qorbani M,
19 Quintanilla BPA, Radfar A, Rafay A, Rahimi-Movaghar V, Rahman MHU, Rahman M, Rai RK, Ranabhat CL,
20 Rankin Z, Rao PC, Rath GK, Rawaf S, Ray SE, Rehm J, Reiner RC, Reitsma MB, Remuzzi G, Rezaei S, Rezai
21 MS, Rokni MB, Ronfani L, Roshandel G, Roth GA, Rothenbacher D, Ruhago GM, Sa R, Saadat S, Sachdev
22 PS, Sadat N, Safdarian M, Safi S, Safiri S, Sagar R, Sahathevan R, Salama J, Salamati P, Salomon JA, Samy
23 AM, Sanabria JR, Sanchez-Niño MD, Santomauro D, Santos IS, Santric Milicevic MM, Sartorius B,
24 Satpathy M, Schmidt MI, Schneider IJC, Schulhofer-Wohl S, Schutte AE, Schwebel DC, Schwendicke F,
25 Sepanlou SG, Servan-Mori EE, Shackelford KA, Shahrzad S, Shaikh MA, Shamsipour M, Shamsizadeh M,
26 Sharma J, Sharma R, She J, Sheikhbahaei S, Shey M, Shi P, Shields C, Shigematsu M, Shiri R, Shirude S,
27 Shiue I, Shoman H, Shrimme MG, Sigfusdottir ID, Silpakit N, Silva JP, Singh JA, Singh A, Skiadaresi E, Sligar
28 A, Smith DL, Smith A, Smith M, Sobaih BHA, Soneji S, Sorensen RJD, Soriano JB, Sreeramareddy CT,
29 Srinivasan V, Stanaway JD, Stathopoulou V, Steel N, Stein DJ, Steiner C, Steinke S, Stokes MA, Strong M,
30 Strub B, Subart M, Sufiyan MB, Sunguya BF, Sur PJ, Swaminathan S, Sykes BL, Tabarés-Seisdedos R,
31 Tadakamadla SK, Takahashi K, Takala JS, Talongwa RT, Tarawneh MR, Tavakkoli M, Taveira N, Tegegne
32 TK, Tehrani-Banihashemi A, Temsah M-H, Terkawi AS, Thakur JS, Thamsuwan O, Thankappan KR,

- 1 Thomas KE, Thompson AH, Thomson AJ, Thrift AG, Tobe-Gai R, Topor-Madry R, Torre A, Tortajada M,
2 Towbin JA, Tran BX, Troeger C, Truelsen T, Tsoi D, Tuzcu EM, Tyrovolas S, Ukwaja KN, Undurraga EA,
3 Updike R, Uthman OA, Uzochukwu BSC, van Boven JFM, Vasankari T, Venketasubramanian N, Violante
4 FS, Vlassov VV, Vollset SE, Vos T, Wakayo T, Wallin MT, Wang Y-P, Weiderpass E, Weintraub RG, Weiss
5 DJ, Werdecker A, Westerman R, Whetter B, Whiteford HA, Wijeratne T, Wiysonge CS, Woldeyes BG,
6 Wolfe CDA, Woodbrook R, Workicho A, Xavier D, Xiao Q, Xu G, Yaghoubi M, Yakob B, Yano Y, Yaseri M,
7 Yimam HH, Yonemoto N, Yoon S-J, Yotebieng M, Younis MZ, Zaidi Z, Zaki MES, Zegeye EA, Zenebe ZM,
8 Zerfu TA, Zhang AL, Zhang X, Zipkin B, Zodpey S, Lopez AD, Murray CJL. Global, regional, and national
9 age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global
10 Burden of Disease Study 2016. *The Lancet* 2017;**390**(10100):1151-1210.
- 11 2. Giampaoli S, Palmieri L, Donfrancesco C, Lo Noce C, Pilotto L, Vanuzzo D. Cardiovascular health
12 in Italy. Ten-year surveillance of cardiovascular diseases and risk factors: Osservatorio Epidemiologico
13 Cardiovascolare/Health Examination Survey 1998-2012. *Eur J Prev Cardiol* 2015;**22**(2 Suppl):9-37.
- 14 3. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida
15 JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH,
16 Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad
17 S, Tsioufis KP, van Dis I, van Gelder IC, Wannan C, Williams B. 2021 ESC Guidelines on cardiovascular
18 disease prevention in clinical practice. *Eur J Prev Cardiol* 2022;**29**(1):5-115.
- 19 4. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton
20 AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL,
21 Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-
22 Solà J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N,
23 Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P,
24 Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma
25 M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundström J, Timpel P,
26 Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C, Fuster V, Roth GA, Mensah
27 GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton A, Benjamin EJ, Benziger
28 CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis JR, Catapano AL, Chugh S, Cooper LT, Coresh J,
29 Criqui MH, DeCleene NK, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-Sola J, Fowkes FGR, Gakidou E,
30 Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum NJ, Koroshetz WJ, Lavie C, Lloyd-
31 Jones D, Lu HS, Mirijello A, Misganaw AT, Mokdad AH, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe

1 M, Oliveira GMM, Otto CM, Owolabi MO, Pratt M, Rajagopalan S, Reitsma MB, Ribeiro ALP, Rigotti NA,
2 Rodgers A, Sable CA, Shakil SS, Sliwa K, Stark BA, Sundström J, Timpel P, Tleyjeh II, Valgimigli M, Vos T,
3 Whelton PK, Yacoub M, Zuhlke LJ, Abbasi-Kangevari M, Abdi A, Abedi A, Aboyans V, Abrha WA, Abu-
4 Gharbieh E, Abushouk AI, Acharya D, Adair T, Adebayo OM, Ademi Z, Advani SM, Afshari K, Afshin A,
5 Agarwal G, Agasthi P, Ahmad S, Ahmadi S, Ahmed MB, Aji B, Akalu Y, Akande-Sholabi W, Aklilu A,
6 Akunna CJ, Alahdab F, Al-Eyadhy A, Alhabib KF, Alif SM, Alipour V, Aljunid SM, Alla F, Almasi-Hashiani A,
7 Almustanyir S, Al-Raddadi RM, Amegah AK, Amini S, Aminorroaya A, Amu H, Amugsi DA, Ancuceanu R,
8 Anderlini D, Andrei T, Andrei CL, Ansari-Moghaddam A, Anteneh ZA, Antonazzo IC, Antony B, Anwer R,
9 Appiah LT, Arabloo J, Ärnlöv J, Artanti KD, Ataro Z, Ausloos M, Avila-Burgos L, Awan AT, Awoke MA,
10 Ayele HT, Ayza MA, Azari S, B DB, Baheiraei N, Baig AA, Bakhtiari A, Banach M, Banik PC, Baptista EA,
11 Barboza MA, Barua L, Basu S, Bedi N, Béjot Y, Bennett DA, Bensenor IM, Berman AE, Bezabih YM,
12 Bhagavathula AS, Bhaskar S, Bhattacharyya K, Bijani A, Bikbov B, Birhanu MM, Bloor A, Brant LC,
13 Brenner H, Briko NI, Butt ZA, Caetano dos Santos FL, Cahill LE, Cahuana-Hurtado L, Cámara LA, Campos-
14 Nonato IR, Cantu-Brito C, Car J, Carrero JJ, Carvalho F, Castañeda-Orjuela CA, Catalá-López F, Cerin E,
15 Charan J, Chattu VK, Chen S, Chin KL, Choi J-YJ, Chu D-T, Chung S-C, Cirillo M, Coffey S, Conti S, Costa VM,
16 Cundiff DK, Dadras O, Dagnew B, Dai X, Damasceno AAM, Dandona L, Dandona R, Davletov K, De la Cruz-
17 Góngora V, De la Hoz FP, De Neve J-W, Denova-Gutiérrez E, Derbew Molla M, Derseh BT, Desai R,
18 Deuschl G, Dharmaratne SD, Dhimal M, Dhungana RR, Dianatinasab M, Diaz D, Djalalinia S, Dokova K,
19 Douiri A, Duncan BB, Duraes AR, Eagan AW, Ebtehaj S, Eftekhari A, Eftekhazadeh S, Ekholuenetale M, El
20 Nahas N, Elgendy IY, Elhadi M, El-Jaafary SI, Esteghamati S, Etillo AE, Eyawo O, Fadhil I, Faraon EJA, Faris
21 PS, Farwati M, Farzadfar F, Fernandes E, Fernandez Prendes C, Ferrara P, Filip I, Fischer F, Flood D,
22 Fukumoto T, Gad MM, Gaidhane S, Ganji M, Garg J, Gebre AK, Gebregiorgis BG, Gebregzabiher KZ,
23 Gebremeskel GG, Getacher L, Obsa AG, Ghajar A, Ghashghaee A, Ghith N, Giampaoli S, Gilani SA, Gill PS,
24 Gillum RF, Glushkova EV, Gnedovskaya EV, Golechha M, Gonfa KB, Goudarzian AH, Goulart AC,
25 Guadamuz JS, Guha A, Guo Y, Gupta R, Hachinski V, Hafezi-Nejad N, Haile TG, Hamadeh RR, Hamidi S,
26 Hankey GJ, Hargono A, Hartono RK, Hashemian M, Hashi A, Hassan S, Hassen HY, Havmoeller RJ, Hay SI,
27 Hayat K, Heidari G, Herteliu C, Holla R, Hosseini M, Hosseinzadeh M, Hostiuc M, Hostiuc S, Househ M,
28 Huang J, Humayun A, Iavicoli I, Ibeneme CU, Ibitoye SE, Ilesanmi OS, Ilic IM, Ilic MD, Iqbal U, Irvani SSN,
29 Islam SMS, Islam RM, Iso H, Iwagami M, Jain V, Javaheri T, Jayapal SK, Jayaram S, Jayawardena R,
30 Jeemon P, Jha RP, Jonas JB, Jonnagaddala J, Joukar F, Jozwiak JJ, Jürisson M, Kabir A, Kahlon T, Kalani R,
31 Kalhor R, Kamath A, Kamel I, Kandel H, Kandel A, Karch A, Kasa AS, Katoto PDMC, Kayode GA, Khader YS,
32 Khammarnia M, Khan MS, Khan MN, Khan M, Khan EA, Khatab K, Kibria GMA, Kim YJ, Kim GR, Kimokoti

1 RW, Kisa S, Kisa A, Kivimäki M, Kolte D, Koolivand A, Korshunov VA, Koulmane Laxminarayana SL,
2 Koyanagi A, Krishan K, Krishnamoorthy V, Kuate Defo B, Kucuk Bicer B, Kulkarni V, Kumar GA, Kumar N,
3 Kurmi OP, Kusuma D, Kwan GF, La Vecchia C, Lacey B, Lallukka T, Lan Q, Lasrado S, Lassi ZS, Lauriola P,
4 Lawrence WR, Laxmaiah A, LeGrand KE, Li M-C, Li B, Li S, Lim SS, Lim L-L, Lin H, Lin Z, Lin R-T, Liu X, Lopez
5 AD, Lorkowski S, Lotufo PA, Lugo A, M NK, Madotto F, Mahmoudi M, Majeed A, Malekzadeh R, Malik AA,
6 Mamun AA, Manafi N, Mansournia MA, Mantovani LG, Martini S, Mathur MR, Mazzaglia G, Mehata S,
7 Mehendiratta MM, Meier T, Menezes RG, Meretoja A, Mestrovic T, Miazgowski B, Miazgowski T,
8 Michalek IM, Miller TR, Mirrakhimov EM, Mirzaei H, Moazen B, Moghadaszadeh M, Mohammad Y,
9 Mohammad DK, Mohammed S, Mohammed MA, Mokhayeri Y, Molokhia M, Montasir AA, Moradi G,
10 Moradzadeh R, Moraga P, Morawska L, Moreno Velásquez I, Morze J, Mubarak S, Muruet W, Musa KI,
11 Nagarajan AJ, Nalini M, Nangia V, Naqvi AA, Narasimha Swamy S, Nascimento BR, Nayak VC, Nazari J,
12 Nazarzadeh M, Negoï RI, Neupane Kandel S, Nguyen HLT, Nixon MR, Norrving B, Noubiap JJ, Nouthe BE,
13 Nowak C, Odukoya OO, Ogbo FA, Olagunju AT, Orru H, Ortiz A, Ostroff SM, Padubidri JR, Palladino R,
14 Pana A, Panda-Jonas S, Parekh U, Park E-C, Parvizi M, Pashazadeh Kan F, Patel UK, Pathak M, Paudel R,
15 Pepito VCF, Perianayagam A, Perico N, Pham HQ, Pilgrim T, Piradov MA, Pishgar F, Podder V, Polibin RV,
16 Pourshams A, Pribadi DRA, Rabiee N, Rabiee M, Radfar A, Rafiei A, Rahim F, Rahimi-Movaghar V, Ur
17 Rahman MH, Rahman MA, Rahmani AM, Rakovac I, Ram P, Ramalingam S, Rana J, Ranasinghe P, Rao SJ,
18 Rathi P, Rawal L, Rawasia WF, Rawassizadeh R, Remuzzi G, Renzaho AMN, Rezapour A, Riahi SM,
19 Roberts-Thomson RL, Roever L, Rohloff P, Romoli M, Roshandel G, Rwegerera GM, Saadatagah S, Saber-
20 Ayad MM, Sabour S, Sacco S, Sadeghi M, Saeedi Moghaddam S, Safari S, Sahebkar A, Salehi S,
21 Salimzadeh H, Samaei M, Samy AM, Santos IS, Santric-Milicevic MM, Sarrafzadegan N, Sarveazad A,
22 Sathish T, Sawhney M, Saylan M, Schmidt MI, Schutte AE, Senthilkumaran S, Sepanlou SG, Sha F, Shahabi
23 S, Shahid I, Shaikh MA, Shamali M, Shamsizadeh M, Shawon MSR, Sheikh A, Shigematsu M, Shin M-J,
24 Shin JI, Shiri R, Shiue I, Shuval K, Siabani S, Siddiqi TJ, Silva DAS, Singh JA, Mtech AS, Skryabin VY,
25 Skryabina AA, Soheili A, Spurlock EE, Stockfelt L, Stortecky S, Stranges S, Suliankatchi Abdulkader R,
26 Tadbiri H, Tadesse EG, Tadesse DB, Tajdini M, Tariqujjaman M, Teklehaimanot BF, Temsah M-H, Tesema
27 AK, Thakur B, Thankappan KR, Thapar R, Thrift AG, Timalsina B, Tonelli M, Touvier M, Tovani-Palone MR,
28 Tripathi A, Tripathy JP, Truelsen TC, Tsegay GM, Tsegaye GW, Tsilimparis N, Tusa BS, Tyrovolas S,
29 Umapathi KK, Unim B, Unnikrishnan B, Usman MS, Vaduganathan M, Valdez PR, Vasankari TJ, Velazquez
30 DZ, Venketasubramanian N, Vu GT, Vujcic IS, Waheed Y, Wang Y, Wang F, Wei J, Weintraub RG,
31 Weldemariam AH, Westerman R, Winkler AS, Wiysonge CS, Wolfe CDA, Wubishet BL, Xu G, Yadollahpour
32 A, Yamagishi K, Yan LL, Yandrapalli S, Yano Y, Yatsuya H, Yeheyis TY, Yeshaw Y, Yilgwan CS, Yonemoto N,

- 1 Yu C, Yusefzadeh H, Zachariah G, Zaman SB, Zaman MS, Zamanian M, Zand R, Zandifar A, Zarghi A,
2 Zastrozhin MS, Zastrozhina A, Zhang Z-J, Zhang Y, Zhang W, Zhong C, Zou Z, Zuniga YMH, Murray CJL,
3 Fuster V. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD
4 2019 Study. *Journal of the American College of Cardiology* 2020;**76**(25):2982-3021.
- 5 5. Laufs U, Wassmann S, Czech T, Münzel T, Eisenhauer M, Böhm M, Nickenig G. Physical Inactivity
6 Increases Oxidative Stress, Endothelial Dysfunction, and Atherosclerosis. *Arteriosclerosis, Thrombosis,
7 and Vascular Biology* 2005;**25**(4):809-814.
- 8 6. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease,
9 and frailty. *Nature Reviews Cardiology* 2018;**15**(9):505-522.
- 10 7. Fioranelli M, Bottaccioli AG, Bottaccioli F, Bianchi M, Rovesti M, Rocchia MG. Stress and
11 Inflammation in Coronary Artery Disease: A Review Psychoneuroendocrineimmunology-Based. *Front
12 Immunol* 2018;**9**:2031.
- 13 8. Fortuin-de Smidt MC, Sewe MO, Lassale C, Weiderpass E, Andersson J, Huerta JM, Ekelund U,
14 Aleksandrova K, Tong TY, Dahm CC, Tjønneland A, Kyrø C, Steindorf K, Schulze MB, Katzke V, Sacerdote
15 C, Agnoli C, Masala G, Tumino R, Panico S, Boer JM, Onland-Moret NC, Wendel-Vos GW, van der Schouw
16 YT, Borch KB, Agudo A, Petrova D, Chirilaque MD, Conchi MI, Amiano P, Melander O, Heath AK, Aune D,
17 Forouhi NG, Langenberg C, Brage S, Riboli E, Wareham NJ, Danesh J, Butterworth AS, Wennberg P.
18 Physical activity attenuates but does not eliminate coronary heart disease risk amongst adults with risk
19 factors: EPIC-CVD case-cohort study. *Eur J Prev Cardiol* 2022.
- 20 9. Mok A, Khaw KT, Luben R, Wareham N, Brage S. Physical activity trajectories and mortality:
21 population based cohort study. *Bmj* 2019;**365**:l2323.
- 22 10. Gonzalez-Jaramillo N WM, Arango-Rivas A, Gonzalez-Jaramillo V, Mesa-Vieira C, Minder B,
23 Franco OH, Bano A. Systematic Review of Physical Activity Trajectories and Mortality in Patients With
24 Coronary Artery Disease. *J Am Coll Cardiol* 2022;**79**(17):1690-1700.

25

26