







# BMJ Open Running on empty: a longitudinal global study of psychological well-being among runners during the COVID-19 pandemic

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## ABSTRACT

**Objectives** There are indications that the COVID-19 pandemic has had a profound negative effect on psychological well-being. Here, we investigated this hypothesis using longitudinal data from a large global cohort of runners, providing unprecedented leverage for understanding how the temporal development in the pandemic pressure relates to well-being across countries.

**Design** Prospective cohort study.

**Setting** Global.

**Participants** We used data from the worldwide Garmin-RUNSAFE cohort that recruited runners with a Garmin Connect account, which is used for storing running activities tracked by a Garmin device. A total of 7808 Garmin Connect users from 86 countries participated.

**Primary and secondary outcome measures** From 1 August 2019 (prepandemic) to 31 December 2020, participants completed surveys every second week that included the five-item WHO Well-Being Index (WHO-5). Pandemic pressure was proxied by the number of COVID-19-related deaths per country, retrieved from the Coronavirus Resource Centre at Johns Hopkins University. Panel data regression including individual- and time-fixed effects was used to study the association between country-level COVID-19-related deaths over the past 14 days and individual-level self-reported well-being over the past 14 days.

**Results** The 7808 participants completed a total of 125 409 WHO-5 records over the study period. We found a statistically significant inverse relationship between the number of COVID-19-related deaths and the level of psychological well-being—independent of running activity and running injuries (a reduction of 1.42 WHO-5 points per COVID-19-related death per 10 000 individuals,  $p < 0.001$ ).

**Conclusions** This study suggests that the COVID-19 pandemic has had a negative effect on the psychological well-being of the affected populations, which is concerning from a global mental health perspective.

## INTRODUCTION

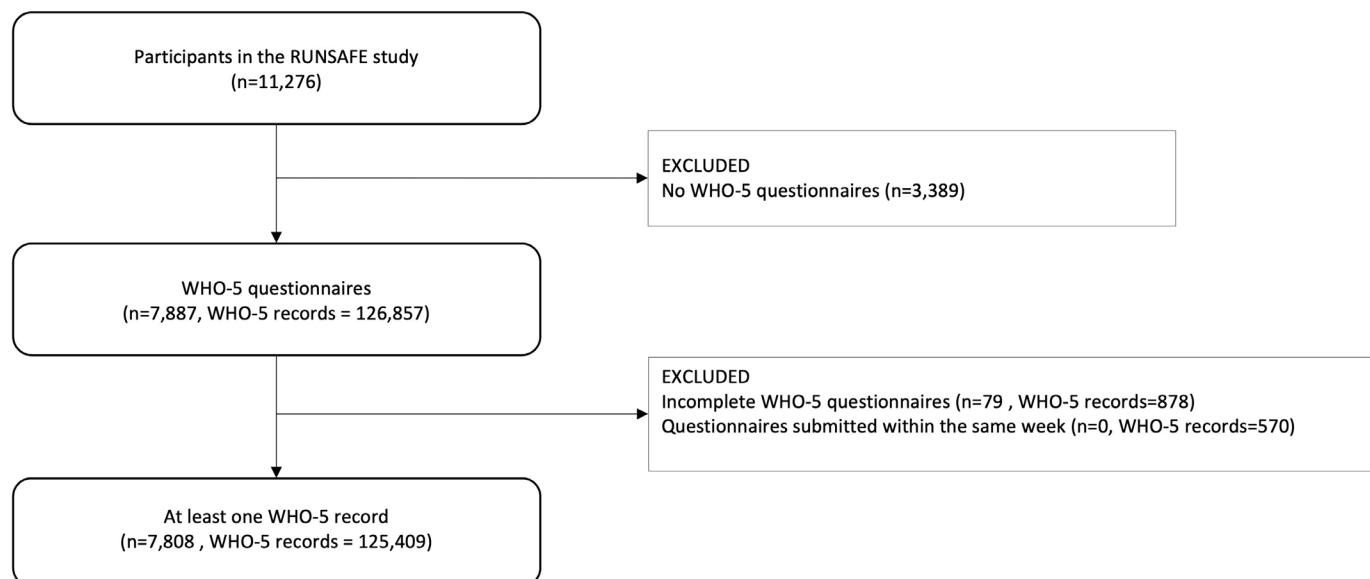
Beyond its obvious negative health consequences for those directly infected with coronavirus, the COVID-19 pandemic—and the ensuing public health measures implemented

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Psychological well-being was tracked every second week over several months prior to and during the COVID-19 pandemic.
- ⇒ The study was based on data from 7808 participants representing 86 countries.
- ⇒ The participants were self-enrolled runners, who are likely more psychologically robust than the general population.
- ⇒ Data on nationwide and regional lockdowns from the 86 countries were not available.

to prevent its spreading (eg, lockdowns and restrictions on social gatherings)—is likely to have had adverse effects on psychological well-being more broadly due to, inter alia, the uncertainty, the disruption of everyday routines, and the social disconnectedness it has induced.<sup>1 2</sup>

Previous longitudinal studies, tracking the development in psychological well-being over time by means of surveys, have provided initial evidence documenting the negative consequences of the COVID-19 pandemic. While informative, these studies generally suffer from one or more significant drawbacks. First, only a subset of these studies has a prepandemic baseline measurement that is necessary to enable any inferences about the consequences of the pandemic.<sup>3–12</sup> Further, even if prepandemic benchmarks are available, they are typically few and dating back a longer period of time (often years) before the onset of the pandemic.<sup>4–14</sup> This compromises the value of the prepandemic measure, and, by implication, the credibility of any observed change in well-being after the onset of the pandemic. Several pre-pandemic measurements taken over a period leading directly up to the pandemic, would strengthen the case



**Figure 1** Flow chart of the study population and WHO-5 observations. WHO-5, five-item WHO Well-Being Index.

further for the pandemic causing an observed decline in psychological well-being. Second, beyond the consequences of the COVID-19 pandemic in toto, previous studies—including our own<sup>13 15–17</sup>—have produced limited knowledge about how psychological well-being covaries with pandemic pressure (ie, the severity of the COVID-19 pandemic) given the absence of systematic post-pandemic measurements of well-being. If psychological well-being changes in tandem with the ebb and tide of the pandemic waves, it strengthens the claim of the pandemic influencing well-being. Third, the existing results are typically from single-country studies.<sup>3 9 18 19</sup> While this is a natural starting point, this means that any (inverse) correspondence between pandemic pressure and psychological well-being could be due to other temporal changes that causes changes in well-being (eg, seasonal changes in daylight or weather).<sup>16 20</sup> Using data from several countries with variation in pandemic pressure and seasonal conditions can alleviate this concern, and would therefore lend further credibility to the robustness of the negative effect of the pandemic pressure on psychological well-being.

Against the backdrop of previous studies and their shortcomings, the aim of this study was to investigate the dose–response relationship between pandemic pressure (proxied by number of COVID-19-related deaths) and psychological well-being using shortly-spaced individual-level panel survey data from more than 80 countries with extensive measurement points both before and after the inception of the pandemic. The data stems from a large global cohort of runners (the Garmin-RUNSAFE Running Health Study<sup>21</sup>), and therefore, to fortify our results against idiosyncratic features of this sample, we used auxiliary data on the participants' running-related characteristics (activities and injuries), to establish that the relationship between the pandemic pressure and psychological well-being is independent of changes in

these characteristics and hence likely generalises more broadly.

## METHODS

### Data source

We used data from the international worldwide Garmin-RUNSAFE Running Health Study that recruited English-speaking runners aged 18+ with a Garmin Connect account. Garmin connect is a tool for storing and sharing running activities from a Garmin device.<sup>21</sup> Enrolment was open from 1 August 2019 (prepandemic) to 31 December 2020. For further details on the recruitment, see Nielsen *et al.*<sup>21</sup>

### Data collection

At enrolment, the participants in the Garmin-RUNSAFE Running Health Study provided information on country of residence and date of birth. Furthermore, they gave access to daily information on running distance (in metres) during follow-up (from enrolment to 31 December 2020) from their Garmin Connect account. From the time of enrolment to 31 December 2020, the RUNSAFE participants were asked to complete surveys every 2 weeks (sent via email) that included the five-item WHO Well-Being Index (WHO-5)<sup>22</sup>—a psychometrically valid and widely used measure of psychological well-being experienced over the past 2 weeks. The five WHO-5 items are: 'I have felt cheerful and in good spirit', 'I have felt calm and relaxed', 'I have felt active and vigorous', 'I woke up feeling fresh and rested' and 'My daily life has been filled with things that interest me'. Each item is scored from 0 (none of the time) to 5 (all the time). The WHO-5 total score is calculated by adding the individual item scores and multiplying by four (ranges from 0 (complete lack of well-being) to 100 (maximum well-being)). The participants also provided weekly information on

**Table 1** Characteristics of the 7808 participants at enrolment

	No of participants (unit)
Sex	
Women, n (%)	1753 (22.5)
Men, n (%)	5935 (76.0)
Missing, n (%)	120 (1.5)
Age, mean years (SD)	
18–24, n (%)	105 (1.3)
25–34, n (%)	788 (10.1)
35–44, n (%)	2227 (28.5)
45–54, n (%)	2841 (36.4)
55–64, n (%)	1372 (17.6)
65–74, n (%)	420 (5.4)
75+, n (%)	42 (0.5)
Missing, n (%)	13 (0.2)
Continent	
Asia*, n (%)	55 (0.7)
Africa†, n (%)	145 (1.9)
North America‡, n (%)	3118 (39.9)
USA, n (%)	2727 (34.9)
Canada, n (%)	370 (4.7)
South America§, n (%)	38 (0.5)
Europe¶, n (%)	4436 (56.8)
UK, n (%)	956 (12.2)
Germany, n (%)	409 (5.2)
Italy, n (%)	382 (4.9)
Denmark, n (%)	376 (4.8)
France, n (%)	334 (4.3)
Netherlands, n (%)	291 (3.7)
Spain, n (%)	282 (3.6)
Sweden, n (%)	282 (3.6)
Norway, n (%)	192 (2.5)
Belgium, n (%)	135 (1.7)
Oceania**, n (%)	16 (0.2)

\*Countries participating in Asia: Taiwan, Qatar, Saudi Arabia, Cambodia, Malaysia, Cyprus, UAE, Turkey, Thailand, Singapore, India, Japan, Israel, Brunei, Lebanon, Indonesia, Hong Kong, China.

†Countries participating in Africa: Sudan, Eswatini, Namibia, Algeria, Egypt, South Africa, Mauritius, Morocco, Uganda, Zimbabwe, Kenya, Reunion.

‡USA and Canada accounts for 99% of the participants from North America. Other participating countries in North America: Panama, Costa Rica, Honduras, British Virgin Islands, Mexico, Dominican Republic, Greenland, Barbados, Guatemala.

§Countries participating in South America: Venezuela, Bolivia, Ecuador, Argentina, Peru, Chile, Falkland Islands, Brazil, Colombia, French Guiana.

¶The 10 countries in Europe with the highest number of participants. These 10 countries accounts for 82% of the participants from Europe. Other participating countries in Europe: Luxembourg, Slovenia, Portugal, Romania, Austria, Croatia, Switzerland, Ireland, Bosnia and Herzegovina, Iceland, Russia, Ukraine, Finland, Faroe Islands, Lithuania, Slovakia, Montenegro, Malta, Greece, Czechia, Serbia, Poland.

\*\*Countries participating in Oceania: French Polynesia, New Zealand, Australia.

running-related injuries/problems. Specifically, they were asked to indicate which day in the past week a running-related injury/problem interfered with their running activity and/or affected their activities of daily living.

### Patient or public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

### Study population

For this study, we used data from all participants in the Garmin-RUNSAFE Running Health Study with information on country of residence and with  $\geq 1$  completed WHO-5 questionnaire on psychological well-being.

### Data on COVID-19-related deaths

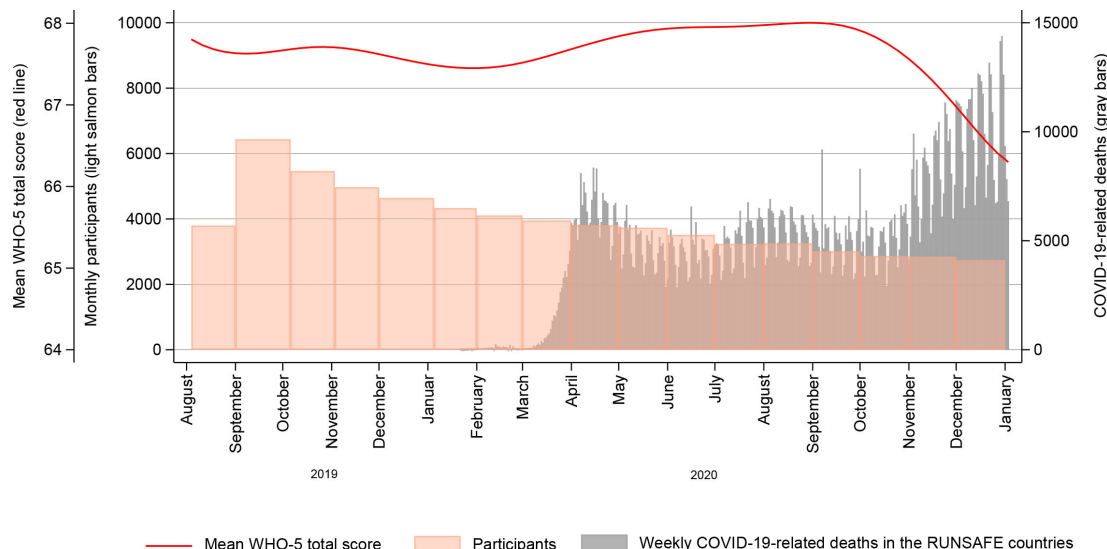
The daily number of COVID-19-related deaths per country was retrieved from the Coronavirus Resource Centre at John Hopkins University.<sup>23</sup> The few instances (0.19%) of negative daily deaths (due to changing definitions) were replaced by the mean number of deaths from the two neighbouring dates. We opted for using country-specific death rates because it, unlike other measures, presumably is highly comparable within countries over time. Other measures like incidence rates of COVID-19 and transmissibility depends heavily on test rates, which varied substantially within countries over time due to variation in availability of tests, pandemic pressure etc.

### Statistical analysis

The data described above were organised in person-week units. Specifically, for each week in the follow-up period (1 August 2019–31 December 2020), we computed participant-level WHO-5 total scores (ie, their well-being the past 14 days), running distance over the past 14 days (in metres), running-related injuries/problems (days affected of the past 14 days), as well as the number of COVID-19-related deaths per 10 000 inhabitants (in the country of the participant) for the past 14 days. The rationale behind the weekly and not 2 weekly organisation was that even though the WHO-5 questionnaires were sent out every second week, responses were returned throughout the subsequent 14-day deadline period. If a participant filled in the WHO-5 twice within the same week, the last WHO-5 total score was used.

The following analyses were carried out: First, the cohort was characterised using descriptive statistics. Subsequently, the relationship between country-level COVID-19-related deaths over the past 14 days and the level of psychological well-being over the past 14 days (WHO-5 total score) was assessed via a linear regression model including individual- and time-fixed effects, which reduces the risk of confounding from stable individual- and country-level characteristics as well as general trends in well-being during the study period:

$$WHO5_{it} = \beta_0 + \beta_1 Deaths_{it} + \beta_2 RunningActivity_{it} + \beta_3 Injury_{it} + a_i + u_t + \epsilon_{it}$$

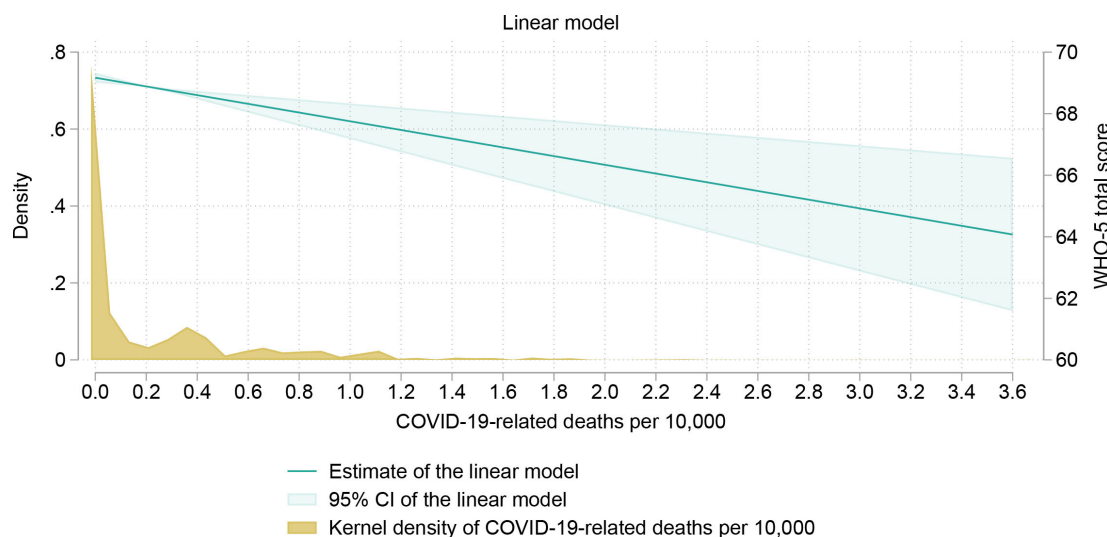


**Figure 2** Number of participants (orange bars), COVID-19 deaths (grey bars) and mean WHO-5 total score (red line) over the course of the study. The line representing the mean WHO-5 total score is generated using a loess smoother. The orange bars represent the number of participants having completed the WHO-5 at least once in the specific month. WHO-5, five-item WHO Well-Being Index.

Here,  $WHO-5_{it}$  is the WHO-5 total score for individual  $i$  for the time period  $t$  (past 14 days),  $Deaths_{it}$  is the number of deaths per 10 000 inhabitants in  $i$ 's country of residence over the time period  $t$ ,  $RunningActivity_{it}$  is  $i$ 's running activity (total metres) over time period  $t$ , and  $injury_{it}$  is the number of days over time period  $t$  where  $i$ 's activity was affected by a running-related injury/problem. The three remaining terms represent unobserved factors affecting the WHO-5 total score:  $a_i$  is time-invariant and individual-specific,  $u_t$  is individual-invariant and time-specific, and  $\epsilon_{it}$  represents unobserved determinants of the WHO-5 total score that vary across both individual and time. To remove  $a_i$  we included a full set of individual-level fixed effects, and to remove  $u_t$  we included time-fixed effects. Subsequently, we ran the same analysis for each of the five WHO-5 items (replacing  $WHO-5_{it}$  in the

equation shown above). The rationale behind this analytical model is illustrated in the directed acyclic graph shown in online supplemental figure 1. To check the robustness of the model, we conducted leave-one-out analysis excluding one country from the model at the time. As secondary analyses, to explore potential non-linear effects of the number of COVID-19-related deaths, square root, natural logarithmic and quadratic terms were employed (see online supplemental methods for further description).

Finally, to test whether the RUNSAFE participants had higher psychological well-being than the general population (a priori hypothesis), we compared the WHO-5 total scores of the Danish RUNSAFE participants with the WHO-5 total scores from the first three waves of the COVID-19 Consequences Denmark Panel Survey



**Figure 3** The association between COVID-19-related deaths per 10 000 and psychological well-being (WHO-5 total score). WHO-5, five-item WHO Well-Being Index.

**Table 2** Individual fixed-effects linear-regression analyses with time fixed effects (crude\* and adjusted† model)

	Regression coefficient ( $\beta_1 Deaths_{it}$ ) (95% CI)	P value
Crude model*		
WHO-5 total score	-1.48 (-2.47 to -0.49)	0.004
Individual WHO-5 item scores (0–20)		
Interest	-0.40 (-0.63 to -0.17)	<0.001
Fresh	-0.20 (-0.35 to -0.05)	0.011
Vigorous	-0.25 (-0.52 to 0.01)	0.061
Relaxed	-0.25 (-0.39 to -0.11)	<0.001
Cheerful	-0.38 (-0.63 to -0.13)	0.003
Adjusted model†		
WHO-5 total score	-1.42 (-2.16 to -0.67)	<0.001
Individual WHO-5 item scores (0–20)		
Interest	-0.40 (-0.60 to -0.20)	<0.001
Fresh	-0.20 (-0.30 to -0.10)	<0.001
Vigorous	-0.20 (-0.39 to 0.02)	0.032
Relaxed	-0.27 (-0.40 to -0.15)	<0.001
Cheerful	-0.34 (-0.55 to -0.13)	0.002

\*Observations: 125 409. Individuals: 7808. Model:  
 $WHO5_{it} = \beta_0 + \beta_1 Deaths_{it} + a_i + u_t + \epsilon_{it}$ .  
 †Observations: 84 679. Individuals: 6222. Model:  
 $WHO5_{it} = \beta_0 + \beta_1 Deaths_{it} + \beta_2 RunningActivity_{it} + \beta_3 Injury_{it} + a_i + u_t + \epsilon_{it}$  where  
 $Deaths_{it}$  is a numerical discrete variable measuring the number of deaths per 10 000 inhabitants (cf. table 1) in  $i$ 's country of residence at time period  $t$  ( $t$  represents periods of 14 days),  
 $RunningActivity_{it}$  is a continuous variable measuring  $i$ 's running activity (total meters) at time period  $t$ ,  $Injury_{it}$  measures the number of days where  $i$ 's activity was affected by a running injury or problem at time period  $t$ . The three remaining terms represent unobserved factors affecting  $WHO5_{it}$ :  $a_i$  is time-invariant and individual-specific;  $u_t$  is unit-invariant and time-specific; and  $\epsilon_{it}$  represents unobserved determinants of  $WHO5_{it}$  that vary across both individual and time. To remove  $a_i$ , we included a full set of individual-level fixed effects, and to remove  $u_t$  we included time-fixed effects.  
 WHO-5, five-item WHO Well-Being Index.

2020.<sup>13 15 16</sup> The WHO-5 total scores from the COVID-19 Consequences Denmark Panel Survey 2020 respondents were weighted on gender, age, education, region and political party choice in the last election in order to render them representative of the Danish population. Only WHO-5 data from overlapping periods of data collection in the two surveys were included, namely 31 March 2020–6 April 2020; 22 April 2020–30 April 2020 and 20 November 2020–8 December 2020.<sup>13 15 16</sup>

All analyses were carried out using Stata V.17.0 (StataCorp) with 0.05 as the threshold for statistical significance.

## RESULTS

In the period from 1 August 2019 to 31 December 2020, a total of 7808 RUNSAFE-participants completed the WHO-5 questionnaire at least once. Data from these 7808

participants were included in the analyses (see figure 1). The characteristics of the participants are listed in table 1.

The participants covered 86 different countries, the age range was 18–88 years, mean age was 47.3 years (SD=10.61) and 76% were men. The maximum follow-up was 17 months including 39 biweekly WHO-5 questionnaires, and 75 weekly injury questionnaires. The total number of completed WHO-5 questionnaires was 125 409 and the median number of completed WHO-5 questionnaires among the 7808 participants was 12 (IQR: 3–31). A total of 980 (12.6%) of the participants had completed the WHO-5 only once and thereby only contributed to the estimation of the country- and the time fixed effects. For an illustration of the distribution of participants and completed WHO-5 questionnaires across countries, see online supplemental figure 2.

Among the 7808 respondents, 7175 (91.9%) had tracked their running activity through Garmin Connect at least once (with a total of 230 169 weeks with information on running activity), and 7759 (99.4%) had filled out the weekly questionnaire about running-related injuries at least once (with a total of 257 171 weeks with information on injuries). For an illustration of the tracking of running activity and completed injury questionnaires over the course of the study, see online supplemental figure 3.

The range in number of COVID-19-related deaths per 10 000 (within a country) during a fourteen-day period was 0 to 3.65 with a median of 0.02 (IQR: 0.00–0.35) in the study period, and a median of 0.31 (IQR: 0.04–0.59) in the period from March 2020 to December 2020. For an illustration of the number of COVID-19-related deaths, the number of study participants, and the level of psychological well-being of these participants over the study period (see figure 2).

The linear association between the number of COVID-19-related deaths per 10 000 and psychological well-being (WHO-5 total score) is illustrated in figure 3 and reported in table 2.

The results show a statistically significant inverse relationship (regression coefficient of -1.42, 95% CI -2.16 to -0.67), which remained when excluding running activity and running related injuries/problems from the model (table 2) and when leaving specific countries out of the analysis one at the time (online supplemental table 1). The number of COVID-19-related deaths was also inversely associated with the five individual WHO-5 items (table 2). The results of the three non-linear analyses were also consistent with an inverse relationship between the number of COVID-19-related deaths per 10 000 and psychological well-being (table 2 and online supplemental table 2). Specifically, all analyses showed that the strength of the inverse relationship decreased at higher levels of COVID-19-related deaths (see online supplemental figure 4). The results of the quadratic model indicated that the relationship could be positive at very high levels of COVID-19 related deaths (approximately  $\geq 2.0$  COVID-19-related deaths per 10 000 inhabitants). This specific



finding is, however, uncertain, because of few observations with very high levels of COVID-19-related deaths (out of the 125 409 person-week observations, only 1974 (1.6%) had a rate  $\geq 2.0$  deaths per 10 000 inhabitants).

Finally, and as expected, the psychological well-being of the participants in the Garmin-RUNSAFE Running Health Study (mean WHO-5 total score of 71.6, 95% CI 70.0 to 73.2) was substantially higher than that of the participants from the COVID-19 Consequences Denmark Panel Survey 2020 (mean WHO-5 total score of 63.2, 95% CI 62.7 to 63.7), when compared across the same time periods.

## DISCUSSION

In this longitudinal study of 7808 runners from 86 countries, we found a statistically significant inverse relationship between the number of COVID-19-related deaths and the level of psychological well-being, which was independent of running activity and running injuries. These results were generally robust across models and sensitivity (leave-one-out) analyses.

To our knowledge, this study is the first to have tracked the psychological well-being of individuals from >80 countries over several months prior to and during the COVID-19 pandemic. The results bolsters and furthers findings from studies using less fine-grained data and less rigorous designs in showing that there is a dynamic inverse relationship between the pandemic pressure and the level of psychological well-being.<sup>3–14</sup> They are also in line with studies having focused on the opposite of psychological well-being during the COVID-19 pandemic, namely symptoms of anxiety and depression, where a positive relationship with the pandemic pressure has been the most consistent finding.<sup>24–28</sup> Irrespective of the definition of outcome, this body of literature clearly suggests that the COVID-19 pandemic is not only a global crisis from a physical health perspective, but also from a mental health/psychological perspective, as acknowledged by the WHO.<sup>29</sup>

Although this study has strengths, in particular due to the availability of fine-grained prepandemic and in-pandemic data on psychological well-being from many countries across continents, there are also important limitations to take into account. First, participants in the survey are self-enrolled and the sample is therefore probably not representative of runners from the included countries, and—given the heterogeneous participation patterns across countries (table 1; online supplemental figure 2)—certainly not representative of the global population of runners. Second, participation varies over time and there are clear signs of panel attrition over the study period, which also raises questions about generalisability. The inclusion of individual fixed effects, and by implication, country fixed effects, alleviates some of this concern, as it removes the influence of individual-level and country-level variables. Nevertheless, generalisability of the results beyond the specific participants is uncertain. Third, and relatedly, the fact that all participants are runners is also

suboptimal with regard to the generalisability of the results. We also notice that the sample is predominantly male (76%), which is likely due to the recruitment method via Garmin Connect—a platform that may be more appealing to male than female runners. Runners are known to be healthier than the general population—both physically and psychologically<sup>30–33</sup>—as also demonstrated by the comparison of psychological well-being between the participants in the Garmin-RUNSAFE Running Health Study and the participants from the COVID-19 Consequences Denmark Panel Survey 2020. However, while runners are not representative of the general population, the fact that they are considered to be quite robust from a psychological perspective, implies that the inverse relationship is likely to be stronger in the general population, thereby rendering our estimate a conservative one. Fourth, with regard to the exposure, namely the number of COVID-19-related deaths, there are inter-country differences in the reporting/operationalisation.<sup>34,35</sup> This does not constitute a major problem, because country differences are removed with the individual-fixed effects. Nevertheless, identical reporting practices would have been preferable. Fifth and relatedly, data on nationwide and regional lockdowns from the 86 countries were not available to us. We were therefore unable to investigate whether the observed negative relationship between COVID-19-related deaths and psychological well-being is driven by the lockdowns—a downstream consequence of pandemic pressure—as has been suggested by some, but not all, other studies.<sup>36,37</sup> Sixth, although the results of this study do not suggest that running activity and running related injuries/problems have marked effects on the impact of the COVID-19 pandemic pressure on psychological well-being, controlled intervention studies are required to clarify the question of causality. Such studies are, however, also associated with challenges—in particular due to the difficulties with regard to blinding, which is virtually impossible. Seventh, our data does not cover the period from 1 January 2021 and onwards, but based on other studies covering this period, it seems that the psychological well-being of people has kept covarying with the pandemic pressure.<sup>17,36</sup> Given that the pandemic pressure is relatively low at the time of writing, it seems reasonable to assume that its negative influence on psychological well-being is correspondingly low.

In conclusion, based on analysis of longitudinal data from 7808 runners from 86 countries, this study substantiates the notion that the COVID-19 pandemic has had a negative impact on the psychological well-being of the affected populations. As the COVID-19 pandemic is ongoing and may develop further due to occurrence of new viral variants, these findings are concerning from a global mental health perspective.

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**Contributors** The study was designed in collaboration between all authors. The analyses were carried out by HTV and KMS. The results were interpreted by all authors. HTV, PT, D, KMS and SDØ wrote the first draft of the manuscript, which was subsequently revised for important intellectual content by RBKB and RØN. All authors approved the final version of the manuscript prior to submission. HTV is the guarantor.

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**Competing interests** SDØ received the 2020 Lundbeck Foundation Young Investigator Prize. Furthermore, SDØ owns units of mutual funds with stock tickers DKIGI and WEKAFKI, as well as units of exchange traded funds with stock tickers TRET and EUNL. The remaining authors report no conflicts of interest.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants but all participants in the Garmin-RUNSAFE Running Health Study completed an online informed consent form prior to enrolment. As this was an observational study, the local ethics committee in the Central Denmark Region waived registration (Request number: 227/2016- Record number: 1-10-72-189-16) in accordance with the Danish Act on Research Ethics Review of Health Research Projects, Section 14, no. 2. The Danish Data Protection Agency approved the study (the Danish Data Protection Agency's record number: 2015-57-0002; Aarhus University's record number: 62908, serial number 309), including the data collection procedure and data storage.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** The data used for the present study cannot be shared as the informed consent specifies that they will be stored only at servers at Aarhus University, Denmark.

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