Tittle: High fragmented physical activity as an early risk indicator of frailty and mortality in adults aged 50 years and over.

Short Tittle: Physical Activity Fragmentation and Frailty

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Abstract

Introduction. This study aimed to explore the associations of activity fragmentation with frailty status and all-cause mortality in a representative US sample of people 50 years and over.

Methods

This prospective study used data from the 2003-2006 waves of the National Health and Nutrition Examination Survey (NHANES). Participants 50 years or over were included in the study (n = 2,586). Frailty status was assessed using a valid modification of the Fried criteria. Linked data from the National Death Index registry were used to ascertain mortality. Physical activity fragmentation was measured by accelerometry. To calculate activity fragmentation, an active-to-sedentary transition probability was calculated as the number of physical activity bouts divided by the total sum of minutes spent in physical activity. Age, gender, ethnicity, education, mobility issues, drinking status, smoking status, bmi, and self-reported chronic diseases were reported in the NHANES study.

Results

An increment of 1SD in activity fragmentation was associated with an increased likelihood of frailty (OR [95%CI] = 1.36 [1.13 to 1.664]). Compared with participants in the *high activity fragmentation*/*low physical activity* category, participants in the *low activity fragmentation/low physical activity* and *low activity fragmentation*/*high physical activity* categories were associated with a lower likelihood of frailty. We found a non-linear association between activity fragmentation and all-cause mortality. Compared with participants in the *high activity fragmentation*/*low physical activity* category, participants in the *low activity fragmentation/low physical activity*, *low activity fragmentation*/*high physical activity*, and *high activity fragmentation*/*high physical activity* category categories were associated with a lower mortality risk. Participants with a low fragmented activity pattern may also overcome some of the detrimental effects associated with sedentary behavior.

Conclusions

Our results suggest that a high fragmented physical activity pattern is associated with frailty and risk of mortality in adults and older adults. This association was independent of total volume of physical activity and time spent sedentary.

Introduction

Frailty is a condition of increased vulnerability [1,2] associated with aging, leading to several adverse health outcomes, including disability, falls, hospitalization, and death [3]. Due to the ageing population, the prevalence of frailty is rising rapidly [3], and the individual burden and costs associated with this condition are sizable [4]. Nonetheless, frailty is dynamic (i.e., individuals move across several states of frailty) and could be prevented to some extent. Therefore, finding strategies to prevent and slow the progression of frailty are of greatest importance [5].

Age, sex, body mass index, education, ethnicity, and the presence of chronic conditions are well-known risk factors for frailty and mortality [6,7]. Lifestyle risk factors such as alcohol or smoking may also contribute to a greater risk of frailty[8]. Insufficient physical activity (i.e., not meeting the physical activity guidelines) and excessive time spent in sedentary activities (i.e., sitting) are well-documented major risk factors for a number of adverse health outcomes [9], including frailty [10]. The patterns of accumulation of physical activity and sedentary behavior may also be relevant [10–12]. Activity fragmentation, defined as the frequency with which a person transitions into a sedentary state from an active state throughout the day, may also contribute to frailty. It is likely that more frail individuals depict a more fragmented pattern of activity, possibly due to an increased fatigue and declines in physical functioning, which may result in the inability to sustain longer bouts of physical activity, and individuals adapting their mobility patterns accordingly [13]. A fragmented pattern of activity has been previously associated with cancer [14], fatigue [15], and subjective memory complaints[16]. Recent evidence has also suggested that more fragmented patterns of physical activity may also be associated with frailty. These previous studies highlight the value of accelerometers to assess physical activity patterns (including activity fragmentation), and to identify adults at risk of becoming frail, even before other clinical manifestations are present. These novel accelerometer metrics may also reveal important insights for the design of tailored interventions to prevent frailty among those at risk. As previously noted, fragmentation in adults may precede declines in functional capability and overall physical activity that typically indicate impeding mortality [17]. However, the dose-response between activity fragmentation and mortality risk remains unexplored. This information can also be useful to identify relevant thresholds of activity fragmentation that may be able to identify plausible impeding health outcomes, previously unknown.

Therefore, this study aimed to explore the associations of activity fragmentation with frailty status and the risk of mortality in a US-based population sample of people 50 years and over. In doing so, we leveraged the potential of accelerometers and, through continuous assessment of minute-by-minute activity as well as sedentary cycles throughout the day, derived a measure of activity fragmentation (i.e., frequency with which a person transitions into a sedentary state from an active state throughout the day) [14]. We hypothesized that a higher activity fragmentation will be associated with greater odds of frailty status and an increased risk of mortality in the study population. We also hypothesized that participants with a low total volume of physical activity and a high fragmented pattern of physical activity will display higher odds of frailty and an increased risk of mortality compared with other patterns of activity.

Methods

Study design and participants

We used data from the waves 2003-2006 of the National Health and Nutrition Examination Survey (NHANES). The NHANES is a series of cross-sectional surveys delivered every two years and is designed to gather health and nutrition information in a representative sample of the civilian, non-institutionalized US population. The original study was approved by the Centers for Disease Control and Prevention Ethics Committee, and all participants gave informed consent. Participants 50 years or over [18] with at least 3 days of valid accelerometry data and available frailty data were included in the study (n = 2,586). Figure 1 shows the flow diagram of participants in the study.

Measures

Frailty status

We defined frailty status based on a modification of the Fried criteria [1], validated for application to NHANES data [19]. The following criteria were used to classify participants' frailty status [18]: exhaustion, defined by ''some difficulty'', ''much difficulty'', or ''unable to do'' when asked how much difficulty they have ''walking from one room to the other on the same level''. Low physical activity, defined as ''less active'' when asked ''Compared with most (men/women) your age, would you say that you are more active, less active, or about the same?''. Weakness, defined by ''some difficulty", ''much difficulty'', or ''unable to do'' when asked how much difficulty they have ''lifting or carrying something as heavy as 10 pounds [like a sack of potatoes or rice]''. Low body weight, defined by BMI 18.5 kg/m^2 or lower. Robust individuals were those with no criteria present. Participants with 1 or 2 criteria were considered pre-frail, and participants with 3 or 4 were considered frail. Because of the low proportion of frail individuals within our sample (4%), the pre-frail and frail groups were merged into a unique category. Participants who did not present any of the aforementioned criteria were classified as robust. Individuals with missing data on any of the criteria were excluded from the study.

Mortality

A subset of the individuals included is linked to death records from the National Death Index until the 31st of December of 2011, which provides information on whether or not the participant was alive at follow-up. If deceased, the length of time (in months) between the NHANES examination and the subject's death is provided, as well as the cause of death.

Accelerometer variables

Physical activity and activity fragmentation were measured by accelerometry. Participants wore accelerometers (AM-7164, ActiGraph, LLC, Fort Walton Beach, Florida) on their waist according to the protocol for 7-consecutive days during waking hours. Accelerometer data reduction in the current study followed validated procedures [20]. Accelerometers were set to record accelerometer counts in one-minute epochs. Non-wear time was defined as 60 consecutive minutes or longer of zero intensity counts, with no more than two minutes of counts between zero and 100. The study included data only from participants with at least 3 valid days with 10 or more hours per day of wear time [14]. Valid accelerometer counts were classified into sedentary (<100 counts/min) or otherwise active (100+ counts/min). Two different continuous measures were then derived. First, to calculate total physical activity volume, activity counts were summed across all minutes for each valid day and averaged across all valid days for each participant. Second, to calculate activity fragmentation, an active-to-sedentary transition probability was calculated as the number of active physical activity bouts divided by the total sum of minutes spent in active physical activity (i.e., consecutive minutes registering 100+ counts/min). We used the sample-based median value of the total volume of physical activity and activity fragmentation to derive high and low physical activity and activity fragmentation groups. Based on these values, we classified participants into four mutually exclusive physical activity pattern categories: low physical activity fragmentation/high physical activity, low physical activity fragmentation/low physical activity, high physical activity fragmentation/high physical activity, and high physical activity fragmentation/low physical activity [14] . We then used the sample-based median value of sedentary behavior and activity fragmentation to derive high and low sedentary behavior and activity fragmentation groups. Based on these values, we created four mutually exclusive sedentary pattern categories: low physical activity fragmentation/high sedentary behavior, low physical activity fragmentation/low sedentary behavior, high physical activity fragmentation/high sedentary behavior, and high physical activity fragmentation/low sedentary behavior.

Covariates

Based on previous literature [6–8]and data availability, the following covariates were selected: A computer-assisted personal interviewing methodology was used to collect in-home information regarding age, gender, ethnicity, education, mobility issues, drinking status (former-never drinker, heavy drinker, moderate drinker, non-drinker), smoking status (never, former, current), and self-reported chronic diseases (Diabetes, Coronary heart disease, Congestive heart failure, Stroke, Cancer) in the NHANES study. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Statistical analysis

We first described the sample characteristics using mean (SD) or frequency (percentage) for continuous and categorical variables respectively.

Frailty

A multivariable ordinal logistic regression model was conducted to examine the cross-sectional associations between total physical activity volume, activity fragmentation, and joint physical activity pattern category (reference, high physical activity fragmentation/low physical activity group) with the probability of frailty. We also tested these associations for joint sedentary behavior patterns (reference, high physical activity fragmentation/high sedentary behavior). The results are reported as odds ratio (OR) and associated 95% Confidence Interval (CI). The magnitude of the association is illustrated through the average marginal effect (AME) and associated 95% CI. For additional interpretability of the results, we standardized the activity fragmentation index by subtracting the population-level mean and dividing by the population-level standard deviation, resulting in a model coefficient that corresponds to one standard deviation change. A locally weighted scatterplot-smoothing curve was used to represent the adjusted estimated probability of frailty associated with total volume of physical activity and activity fragmentation.

Mortality

We used a cox proportional hazard model to estimate the prospective associations between baseline physical activity (and sedentary behavior) patterns and the risk of mortality. Results are displayed as hazard ratios (HRs) of mortality during follow-up, and time-on-study in months was used as the timescale. We assessed the dose-response associations of activity fragmentation (modelled as a continuous exposure) and all-cause mortality using a restricted cubic spline model to allow for potential non-linearity. For the purpose of this analysis, we trimmed observations less than 5% and greater than 95% of the distribution. Then, we pre-specified knots placed at the 10^{th}, 50^{th} (reference), and 90^{th} percentiles of the exposure distribution. We assumed linearity for values below the 10^{th} percentile and for values above the 90^{th} percentile. Departure from linearity was assessed by a Wald test examining the null hypothesis that the coefficient of the second spline was equal to zero. A Cox proportional hazard model was also used to estimate the HRs of mortality associated with the different joint categories of physical activity patterns (reference, high physical activity fragmentation/low physical activity group). Results are reported as HRs with 95% CIs and levels of significance were set at $p < 0.05$.

All models were adjusted for age, sex, ethnicity, education level, smoking status (never, former, current), drinking status (former-never drinker, heavy drinker, moderate drinker, non-drinker), BMI (kg/m^2), mobility issues (yes, no), self-reported diagnosis of diabetes, coronary heart disease, congestive heart failure, stroke, and cancer as well as sedentary time and total wear time. Sample weights were used to account for the complexity of the NHANES design. All analyses were conducted with R software (version 3.5.1). The alpha level was set at 0.05, two-tailed.

Results

Table 1 shows the characteristics of the study participants. Robust individuals were slightly older, mostly male, and had a lower BMI. They were also more educated, healthier, nonsmokers or drinkers, and had less mobility issues. Finally, robust individuals were also more active, and had a less fragmented activity pattern.

Frailty

An increment of 30 min/day of physical activity was associated with a decreased likelihood of frailty (OR [95%CI] = 0.91 [0.87 to 0.94]; AME [95%CI] = –0.014 [–0.019 to –0.009]). In contrast, an increment of 1SD in activity fragmentation was associated with an increased likelihood of frailty (OR [95%CI] = 1.36 [1.13 to 1.664]; AME [95%CI] = 0.048 [0.019 to 0.077]) in the population of the study (Table 2; Figure 2).

Table 3 shows the association between joint physical activity pattern category and frailty. Compared with participants in the *high activity fragmentation*/*low physical activity* category, participants in the *low activity fragmentation/low physical activity* and *low activity fragmentation*/*high physical activity* categories were associated with a lower likelihood of frailty. There was no detectable association between the *high activity fragmentation*/*high physical activity* category and frailty when compared to the *high activity fragmentation*/*low physical activity* category. Compared with participants in the *high activity fragmentation*/*high sedentary behavior* category, other participants in the rest of the joint sedentary behavior pattern groups depicted a lower likelihood of frailty (Table 3)

Mortality

The dose-response analysis revealed a non-linear (*p*-value from second spline 0.040) association between activity fragmentation and all causes of mortality (minimal dose, 23%) (Figure 3). Compared with participants in the *high activity fragmentation*/*low physical activity* category, participants in the *low activity fragmentation/low physical activity*, *low activity fragmentation*/*high physical activity,* and *high activity fragmentation*/*high physical activity* categories were associated with a lower mortality risk (Table 4). A lower mortality risk was also observed for participants in the high activity fragmentation/low sedentary behavior, low activity fragmentation/low sedentary behavior, and low activity fragmentation/high sedentary behavior groups when compared with those participants classified in the high activity fragmentation/high sedentary behavior (Table 4).

Discussion

The current study was designed to examine the association between physical activity fragmentation and frailty in a population of adults from the NHANES survey. Activity fragmentation has already been associated with several clinical outcomes. For example, Palmberg et al. [15] and Wanigatunga et al. [17] found that a higher physical activity fragmentation was associated with an increased risk of mental fatigability and mortality, respectively. Similarly, del Pozo Cruz et al. found that a higher activity fragmentation was associated with subjective memory complaints in older adults [16]. Recent evidence suggested that fragmented patters of physical activity may also be associated with frailty[21]. Our results complement and extend those from previous studies and suggest that adults and older with a fragmented physical activity pattern could be more prone to frailty, over and above total time of physical activity. Similarly, we also found that a more fragmented patter of activity was associated with an increased risk of mortality. Another relevant finding of this study was that a low fragmented activity may be beneficial even in the presence of high volumes of sedentary behavior.

Previous studies have indicated the major role total volume of physical activity and sedentary behavior have on frailty among adults and older adults [22–24]. Others have indicated that patterns of physical activity and sedentary behavior accumulation may also be relevant [10,16]. In agreement with a previous smaller study[21], we found that an increased probability of transitioning from an active state to a sedentary state (i.e., more fragmented patterns of physical activity) may also be associated with an increased risk of frailty. Biologically, these findings could be partly explained by the functional deterioration associated with age, and an increase in time spent in sedentary behaviours [24,25]. This is consistent with previous evidence suggesting that the inability to sustain prolonged bouts of physical activity is associated with fatigability and loss of physical function among older adults, which could ultimately lead to sarcopenia and frailty[26]. As a novelty, we found that even in the presence of high levels of total time of physical activity, participants with a higher fragmentation index had an increased likelihood of being frail. In contrast, lower activity fragmentation may reduce the odds of frailty even in the presence of high volumes of sedentary behavior. Together, our findings and those from previous reports underscore the relevance of assessing the patterns of physical activity accumulation as well as total time of physical activity and sedentary behavior to identify people at risk of frailty and plan interventions accordingly.

Our study also supports previous evidence from well-functioning older adults[17] and confirms, in a representative sample, that more fragmented activity patterns are associated with an increased risk of early mortality, over and above total volume of physical activity. Together, these findings may support the notion that fragmentation in older adults reflects early signs of declines in functional capability and overall physical activity that typically indicate impeding mortality. As a novelty, we also were able to detect a threshold from which activity fragmentation may pose an increased risk for early death (i.e., 23%), which may serve as a target for interventions.

Our study has several strengths. First, we included a large sample of participants with accelerometry from a national health survey. Further, we restricted our analyses to participants with at least 3 days of accelerometry to reflect more accurately the habitual levels of physical activity. A key strength to our study was the novel metric used to understand the pattern of physical activity accumulation beyond total volume. There are several limitations. First, data are cross-sectional and causal inference cannot be claimed (i.e., our estimates may be influenced by reverse causation). Thus, longitudinal studies are warranted to confirm the existence and temporal order in the relationship between physical activity fragmentation and frailty. Nonetheless, this study is useful to generate novel hypotheses. For example, future experiments may want to test whether at equal volumes of physical activity, a less fragmented pattern results in better functional outcomes. Residual confounding may still exist because factors such as psychological and social variables were not accounted for in this study. Also, frailty was assessed based on survey questions, which may be prone to recall and error bias. However, the Fried criteria is a widely used method and it has been validated in the NHANES survey [19]. Individuals included in our analysis were healthier than those that did not provided frailty or valid accelerometry data, which may introduce selection bias.

In summary, our results suggest that a high fragmented physical activity pattern is associated with frailty and mortality in adults and older adults. This association was independent of total time of physical activity and time spent sedentary. Future studies may capitalize on this novel metric to design interventions aimed to prevent adverse health outcomes. Further studies are necessary to confirm our observations and determine the dose-response association between activity fragmentation and frailty in longitudinal studies.

Statements

Statement of Ethics

Study approval statement

The NHANES protocol has been reviewed and approved by the National Center for Health Statistics research ethics review board (Protocol≠2005-06). All participants provided written informed consent. More detailed information about the NHANES can be found on the official website.

Consent to participate statement

All participants provided informed consent and the National Center for Health Statistics Research Ethics Review Board approved all protocols

Conflict of interest

The authors have no conflicts of interest to declare.

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Author Contributions

Jesus del Pozo Cruz: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; visualization; writing-original draft; and writing-review and editing. Borja del Pozo Cruz: Data curation; investigation; project administration; resources; and writing-review and editing. Miguel Angel perez Sousa: Conceptualization; data curation; methodology; project administration; resources; and writing-review and editing. Rosa M Alfonso-Rosa: Conceptualization; formal analysis; methodology; writing-original draft; and writing-review and editing.

Data Availability Statement:

The data that support the findings of this study are openly available in https://wwwn.cdc.gov/nchs/nhanes/. Further enquiries can be directed to the corresponding author

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Figure legends:

Figure 1. Flow diagram of the participants in the study.

Figure 2. Adjusted estimated probability of frailty associated with activity fragmentation. The panel on the left represents a density plot of frequencies of active-to-sedentary transition probabilities across frailty status. The panel on the right represents the locally weighted scatterplot smoothing curve of the adjusted estimated (i.e., fitted values) probability of frailty associated with activity fragmentation.

Figure 3. Adjusted dose-response association between activity fragmentation and all-cause mortality.