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Proposal Title	Association between long-term leisure-time physical activity sustainability and risk of major chronic diseases
Study Population(s)	NHS1 NHS2 HPFS
Server(s) to be used for the analyses	Channing (nantucket)
Background	The WHO Global Action Plan on Physical Activity 2018–2030 set a global target to reduce physical inactivity by 15% by 2030 [1]. Worldwide, 1 in 4 adults has insufficient physical activity [2]. The 2018 US physical activity guidelines recommend a target range of 500 to 1000 MET-minutes per week of moderate-to-vigorous physical activity (i.e., 150 to 300 minutes per week of moderate-intensity physical activity or 75 to 150 minutes of vigorous-intensity physical activity) [3]. Existing extensive evidence demonstrates that greater volumes of moderate-to-vigorous physical activity are associated with reduced risk of weight gain, CVD, type 2 diabetes, dementia, depression, and cancers of the breast, colon, endometrium, esophagus, stomach, lung, and kidney [4-8]. The dose-response relationship between physical activity volumes and major health outcomes is suggested to be curvilinear with moderate certainty [3]. In particular, health benefits are acquired among inactive individuals by reducing inactivity even if they do not reach the target range, and going beyond the target range does not further lead to appreciable risk reduction of major outcomes [3]. However, important gaps in knowledge remain. No studies have ever investigated the sustainability of physical activity - whether physical activity needs to be regularly maintained over years for the benefit to accrue or whether the benefits achieved through provisional physical activity can sustain over time. Such information is needed to inform future guidelines.

Statement of Hypothesis	Sustainable (cumulative durations satisfying the target ≥7.5 MET-hours/week) physical activity is associated with lower risk of major chronic diseases. A sustainable pattern is more beneficial compared to the pattern that includes both inactivity and intense physical activity despite a high total dose.
Is this a Funded Aim?	No
Study Design	Prospective cohort study in HPFS Follow-up period: 1986-2016 Prospective cohort study in NHS Follow-up period: 1980-2016 Prospective cohort study in NHSII Follow-up period: 1989-2017 Baseline Exclusions: a) had a history of cancer, cardiovascular diseases, or diabetes b) missing physical activity Exclusions During Follow-up: a) had incident major CVD, type 2 diabetes, or total cancer b) died
Exposure(s)	- ‘attainment’ indicator variable (whether the person achieved the recommended physical activity level during the past year) in each main questionnaire cycle defined as physical activity ≥7.5 MET-hours/week according to the 2018 Physical Activity Guidelines for Americans [3] - ‘sustainability’ variable (duration of maintaining recommended physical activity level) by summing ‘2 years × attainment' across questionnaire cycles - ‘physical activity years’ reflecting both intensity and duration by summing ‘2 years × dose/volume' across questionnaire cycles *physical activity dose/volume (activity-specific MET–hours per week summed across activities)
Outcome(s)	The primary outcome, major chronic disease, is defined as the first occurrence of incident major CVD (coronary heart disease and stroke), type 2 diabetes, and total cancer. Secondary outcomes are the components of major chronic disease: major CVD, type 2 diabetes, and total cancer. We will also examine physical-activity related cancers including colon cancer, postmenopausal breast cancer, and endometrial cancer according to the findings (evidence level: strong) from WCRF/IARC.
Covariates	age, sex, race, cigarette smoking status and packyear, alcohol drinking, AHEI score, regular aspirin use, family history of cancer, family history of CVD, family history of diabetes, as well as menopausal status, and postmenopausal hormone use for women
Statistical Analysis	Cox proportional-hazards models stratified by age (months), questionnaire cycle (two-year interval), and cohort (only in pooled analyses) will be used to estimate the associations with the risk of the major chronic diseases both compositely and individually. We will assess the HR associated with sustainability

	and physical activity years that are categorized into quintiles, respectively. P for trend will be calculated based on the Wald test by modeling the median values of each quintile as a continuous variable in the multivariable model. Moreover, stratified analyses by age, sex, smoking status, and alcohol consumption will be conducted. To explore the relative importance of physical activity sustainability versus average volume, joint analyses of sustainability (quintiles) and cumulative average volume (<7.5, 7.5-20, 20-35, ≥35 MET hours/week) will be conducted. To overcome reverse causality that participants with subclinical or undiagnosed diseases who are at higher risk of subsequent disease confirmation may be more likely to become inactive, a two-year lag period will be applied between physical activity assessment and time at risk in the sensitivity analysis [9]. As BMI is a possible intermediate factor linking physical activity with the risk of major chronic diseases, we will additionally adjust for cumulative average BMI in the multivariable model as a sensitivity analysis.
Omics Analyses	No
Will you be conducting a GWAS (genome-wide association study)?	No
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