



Original article

# Associations of daily sedentary behavior, physical activity, and sleep with irritable bowel syndrome: A prospective analysis of 362,193 participants

Xu Gao <sup>a,\*</sup>, Sifan Tian <sup>a</sup>, Ninghao Huang <sup>b</sup>, Gang Sun <sup>c</sup>, Tao Huang <sup>b</sup>

<sup>a</sup> Department of Occupational and Environmental Health Sciences, School of Public Health, Peking University, Beijing 100191, China

<sup>b</sup> Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100191, China

<sup>c</sup> Department of Gastroenterology and Hepatology, First Medical Center of People's Liberation Army General Hospital, Beijing 100853, China

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## Abstract

**Background:** Irritable bowel syndrome (IBS) substantially affects quality of life and requires early prevention. This study aimed to elucidate the relationships between IBS and daily behaviors, including sedentary behavior (SB), physical activity (PA), and sleep. In particular, it seeks to identify healthy behaviors to reduce IBS risk, which previous studies have rarely addressed.

**Methods:** Daily behaviors were retrieved from self-reported data of 362,193 eligible UK Biobank participants. Incident cases were determined by self-report or health care data according to Rome IV criteria.

**Results:** A total of 345,388 participants were IBS-free at baseline, during a median follow-up of 8.45 years, 19,885 incident IBS cases were recorded. When examined individually, SB and shorter ( $\leq 7$  h/day) or longer ( $> 7$  h/day) sleep duration were each positively associated with increased IBS risk, and PA was associated with lower IBS risk. The isotemporal substitution model suggested that replacing SB with other activities could provide further protective effects against IBS risk. Among people sleeping  $\leq 7$  h/day, replacing 1 h of SB with equivalent light PA, vigorous PA, or sleep was associated with 8.1% (95% confidence interval (95%CI): 0.901–0.937), 5.8% (95%CI: 0.896–0.991), and 9.2% (95%CI: 0.885–0.932) reduced IBS risk, respectively. For people sleeping  $> 7$  h/day, light and vigorous PA were associated with a 4.8% (95%CI: 0.926–0.978) and a 12.0% (95%CI: 0.815–0.949) lower IBS risk, respectively. These benefits were mostly independent of genetic risk for IBS.

**Conclusion:** SB and unhealthy sleep duration are risk factors for IBS. A promising way to mitigate IBS risk for individuals sleeping  $\leq 7$  h/day and for those sleeping  $> 7$  h/day appears to be by replacing SB with adequate sleep or vigorous PA, respectively, regardless of the genetic predisposition of IBS.

**Keywords:** Irritable bowel syndrome; Isotemporal substitution model; Physical activity; Sedentary behavior; Sleep

## 1. Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder without obvious organic abnormalities, characterized by recurrent abdominal pain or discomfort, altered bowel habits, stool irregularities, and bloating.<sup>1,2</sup> While generally not causing lethal consequences, IBS can greatly disrupt the daily life and work habits of affected individuals and substantially affect quality of life. Recent evidence suggests that IBS is not solely prevalent in young adults; rather, the disease burden is quite high for middle-aged and older adults as well,<sup>3,4</sup> which adds another layer of threat to the quality of life and health in

an aging population. In terms of economic burden, IBS accounted for approximately half of the referrals to gastroenterology clinics; it yielded greater than Euro8 billion in annual healthcare and indirect costs in Europe and USD10 billion in the US.<sup>5</sup> However, due to the heterogeneity of the disease and the multiplicity of putative pathophysiological mechanisms of IBS,<sup>2,6</sup> targeted risk screening and prevention of IBS are currently not applicable.

To date, there is a dearth of studies exploring nonpharmaceutical approaches to lower IBS risk due to the lack of biomarkers and treatments to cure this multifactorial health disorder.<sup>6</sup> Physical activity (PA), defined as any bodily movements produced by skeletal muscles that result in energy expenditure, has been associated with improvement in gas transit and abdominal distension, symptoms that are frequently observed in IBS patients.<sup>6,7</sup> However, the most recent

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\* Corresponding author.

E-mail address: [xu.gao@pku.edu.cn](mailto:xu.gao@pku.edu.cn) (X. Gao).

Cochrane review suggests that the evidence of PA delaying IBS symptom deterioration as observed in clinical trials might have low certainty because of the limited sample size.<sup>8</sup> Large cohort studies are required to provide timely evidence on the association between PA and IBS risk. Sedentary behavior (SB)—which refers to any waking activity done while sitting, reclining, or lying with low energy expenditure ( $\leq 1.5$  metabolic equivalents, METs), including sitting while watching television or using a computer—is gaining recognition as a risk factor for several long-term conditions independent of PA.<sup>9–11</sup> Nevertheless, the associations of PA and SB with IBS have only been observed in cross-sectional studies without further considering the fact that the length of a day is fixed and so potential risk reductions associated with bringing sedentary duration down depend on the activity that displaces SB, such as certain types of PA or sleep. Given sleep quality is also closely related to IBS,<sup>12</sup> another scientific question arises around whether healthy sleep would be an ideal alternative to SB for reducing the risk of IBS. An isothermal substitution paradigm would directly address such questions by theoretically replacing a certain amount of SB time with an equal amount of time spent on different levels of PA or sleep.<sup>13</sup> Additionally, IBS has been shown to be associated with genetic background,<sup>14</sup> but no studies have investigated whether the genetic susceptibility of IBS could interact with the associations between durations of daily behaviors and incident IBS.

Therefore, we explored the prospective associations of the duration of SB, PA, and sleep with the risk of IBS among middle-aged and older participants from the UK Biobank to understand whether the IBS risk during later life could be influenced by SB, PA, and sleep. In particular, we evaluated the potential benefit of replacing SB with light PA (LPA), moderate PA (MPA), vigorous PA (VPA), and sleep using the isothermal substitution model. Leveraging in-depth genetic information, we further examined whether the genetic predisposition to IBS could modify the relationships between different activities and the incidence of IBS.

## 2. Methods

### 2.1. Study design and population

Study design and methods of the UK Biobank have been reported in detail previously.<sup>15</sup> In brief, UK Biobank is a large-scale prospective study with 502,528 participants aged 37–73 years recruited in 2006–2010 at baseline with multiple ongoing follow-ups. During the initial visit, participants provided information on lifestyle and health data, physical measurements, and their biological samples were collected. This study included 362,193 participants with available information on daily behaviors, potential covariates, and IBS prevalence and incidence over a median follow-up of 8.45 years through December 31, 2018 (Supplementary Fig. 1). UK Biobank has approval from the North West Multicenter Research Ethical Committee, and all participants provided written informed consent. This study has been conducted using the UK Biobank Resource under application number 44430.

### 2.2. Definition of IBS

IBS assessment was conducted using the linked hospital admission records (UK Biobank Data-Fields: 41202 and 41204) primarily as well as an ancillary online gastrointestinal health self-assessment questionnaire issued in 2017, which included 169,635 participants. For the hospital records, participants were classified as cases if they had an *International Classification of Diseases*, 9th and 10th editions (ICD-9/10) code of primary or secondary diagnosis for IBS (ICD-9: 564.1; ICD-10: K58). For the ancillary questionnaire, participants whose symptoms fulfilled the Rome IV criteria for IBS based on questionnaire data at the time of reporting (UK Biobank Data-Fields: 21025, 21026, 21027, 21028, 21031, 21032, and 21033) were defined as IBS cases.<sup>16</sup> If participants gave a positive answer to the question “Have you ever been diagnosed with IBS?” in the ancillary questionnaire (UK Biobank Data-Fields: 21024) but were free of IBS at baseline according to hospital records, he/she would be further considered as an incident IBS case, with the incident date as the median date between the date of taking the questionnaire and the baseline date of visiting the examination center.

### 2.3. Assessments of SB, PA, and sleep

SB in leisure time was self-reported and collected using questionnaires at baseline. Participants were asked how many hours in a typical day they spent watching television, using a computer, and driving (UK Biobank Data-Fields: 1070, 1080, and 1090), which are 3 of the most widespread leisure-time SBs in adults. The length of SB was defined as the sum of time spent doing the 3 activities. PA was quantified using the modified short-form International Physical Activity Questionnaire, which assessed the duration and frequency of PA in leisure time. Weekly PA was summarized using the weekly total MET, calculated by multiplying the MET value of activity by the number of PA hours per week. Based on the guideline of the World Health Organization, PA was categorized as LPA ( $<3$  MET), MPA ( $3–<6$  MET), and VPA ( $\geq 6$  MET).<sup>17</sup> The mean hours for each PA category per day were calculated using the total number of minutes spent per week divided by 7 days. Sleep duration in a day was the average duration over the last 4 weeks collected by self-report (UK Biobank Data-Fields: 1060) and expressed as integer values. We treated sleep duration as a piecewise variable with a breakpoint at 7 h, which is considered the threshold of healthy sleep duration; each of the 2 sleeping variables had an approximately linear association with mortality, as previously reported.<sup>18,19</sup>

### 2.4. Data collection and covariates

Information on socio-demographic characteristics, lifestyle factors, and health status at baseline was obtained by standardized questionnaires. We included age, sex, body mass index (BMI), healthy alcohol intake status, years of education ( $<10$  and  $\geq 10$  years), the regular use of pain-relief medications (i.e., aspirin, ibuprofen, and paracetamol) and/or gastrointestinal agents (i.e., ranitidine, omeprazole, and laxatives),

hypertension, coronary heart disease (CHD), diabetes, and Townsend deprivation index. Detailed measurements of the covariates were reported in supplement methods. Observations with any missing values were excluded from this study.

### 2.5. Genetic risk score for IBS

Detailed information about genotyping, data imputation, and quality control in the UK Biobank was briefly described in supplement methods. Based on the availability of imputed single nucleotide polymorphisms (SNPs), we created a genetic risk score (GRS) for IBS using 6 IBS-related SNPs validated in both UK Biobank and 23andMe data and based on the largest and most recent genome-wide association studies (GWASs).<sup>14</sup> Each SNP was recoded as 0, 1, or 2 according to the number of risk alleles, and missing SNP values for individuals were imputed by corresponding mean values. This GRS, based on multiple genes, was calculated and weighted by multiplying the odds ratios (ORs) of each included SNP with the number of risk alleles, summing them, and then dividing by the total effect size. The detailed SNPs were demonstrated in [Supplementary Table 1](#).

### 2.6. Statistical analysis

We first tested the associations of each activity with the prevalence of IBS at baseline using logistic regression models that increasingly adjusted for potential covariates. Model 1 adjusted for age, sex, and ethnicity. Model 2 additionally adjusted for BMI, smoking status, healthy alcohol intake, and years of education. Model 3 additionally adjusted for hypertension, CHD, diabetes, Townsend deprivation index, and taking pain-relief medications and/or gastrointestinal agents.

Subsequently, among baseline IBS-free participants, we evaluated their baseline activity with their incident IBS during follow-up. Three algorithms were implemented to understand the role of SB, PA, and sleep in the development of IBS. First, we tested the independent associations of the durations of SB, LPA, MPA, VPA, and sleep with incident IBS using a Cox regression model for each activity (i.e., independent model). Then, in case longer SB duration increases IBS risk, we simultaneously adjusted for the durations of LPA, MPA, VPA, and sleep in a single partition model to see if additional changes in the 4 behaviors could mitigate the impact of SB on IBS. The third model was the isothermal substitution model, which explored the effect of substituting SB with equal time of the different types of PA or sleep. This model is based on the realistic assumption that an increase in one behavior will be accompanied by a decrease of equivalent duration (isothermal) in another behavior while total time of all behaviors is kept constant.<sup>13,20</sup> This model could be expressed as a basic proportional hazards model as follows:

$$h(t) = h_0(t)\exp(\beta_1 \times \text{LPA} + \beta_2 \times \text{MPA} + \beta_3 \times \text{VPA} + \beta_4 \times \text{sleep} + \beta_5 \times \text{total time} + \beta_6 \times \text{covariates}),$$

where Total time = SB time + total PA time + sleep duration. The  $\beta_1 - \beta_4$  represent the effects of substituting 1 h/day SB with 1 h/day LPA, MPA, VPA, and sleep, respectively. Corresponding dose-response curves for the relationships between different behaviors and the risk of incident IBS were constructed using restricted cubic spline regression.<sup>21</sup>

Finally, we investigated whether the associations between these behaviors and IBS risk were modified by genetic predisposition to IBS. An interaction term between each behavior and continuous GRS was then generated and implemented in the isothermal substitution model. A binary GRS constructed by median was further used to categorize the IBS risk.

Four sensitivity analyses were conducted to evaluate the robustness of primary findings: (a) the isothermal substitution model additionally adjusting for having a healthy diet and for the stress experience over the last 2 years (stress experience over the last 2 years (yes/no) was coded based on the question "In the last 2 years have you experienced any of the following?" with 6 incidences (Data-field 6145)), (b) the isothermal substitution model excluding participants who developed IBS within the first 2 years of follow-up to avoid reverse causation, (c) the isothermal substitution model excluding participants without MVPA at baseline to avoid bias from extreme observations, and (d) the isothermal substitution model by age group to test the robustness of the model in middle-aged and older individuals separately.

SAS Version 9.4 TS1M7 (SAS Institute, Cary, NC, USA) was used to conduct data cleaning and all analyses. A two-sided *p*-value of <0.05 was considered statistically significant.

## 3. Results

### 3.1. Participants' characteristics

As shown in [Table 1](#), participants were mostly white and aged  $56.22 \pm 8.11$  years (mean  $\pm$  SD). About 35.1% of participants were former smokers, and 55.1% never smoked. The majority had >10 years of education (69.5%), and half reported a healthy daily intake of alcohol. About 53.1%, 5.3%, and 4.7% had hypertension, CHD, or diabetes at baseline, respectively, as diagnosed by doctors according to self-reports and medical records. Participants with excessive sedentary time (>6 h/day) were more likely to be overweight or obese individuals, to be current smokers, and to have hypertension, CHD, and diabetes. Although they reported similar sleep duration to other groups, they had much less PA and were more likely to have no MVPA and to take pain-relief medications regularly.

### 3.2. Associations of SB, PA, and sleep with prevalent IBS

At baseline, 16,805 of the total 362,193 participants had IBS. According to the fully adjusted model, SB and shorter ( $\leq 7$  h/day) or longer ( $> 7$  h/day) sleep duration were each positively associated with increased IBS risk, and 3 types of PA were associated with lower IBS risk, albeit that for MPA was not statistically significant ([Table 2](#)). After controlling for potential covariates, individuals without any MVPA had

**Table 1**  
Baseline characteristics of participants in UK Biobank by sedentary time.<sup>a</sup>

Characteristics	Total (n = 362,193)	Sedentary time (h/day)			
		<2.0 (n = 41,425)	2.0 to <4.0 (n = 134,013)	4.0 to ≤6.0 (n = 117,570)	>6.0 (n = 69,185)
Age (year)	56.22 ± 8.11	54.94 ± 8.15	55.75 ± 8.14	56.99 ± 8.01	56.62 ± 8.05
Body mass index (kg/m <sup>2</sup> )					
Underweight or normal weight (<25)	124,383 (34.4%)	21,672 (52.3%)	53,687 (40.1%)	34,359 (29.2%)	14,665 (21.2%)
Overweight (25 to <30)	155,803 (43.0%)	14,687 (35.5%)	56,080 (41.8%)	53,898 (45.8%)	31,138 (45.0%)
Obese (≥30)	82,007 (22.6%)	5066 (12.2%)	24,246 (18.1%)	29,313 (24.9%)	23,382 (33.8%)
Sex (male)	172,286 (47.6%)	14,833 (35.8%)	55,034 (41.1%)	59,654 (50.7%)	42,765 (61.8%)
Race (white)	345,739 (95.5%)	39,043 (94.3%)	128,687 (96.0%)	112,974 (96.1%)	65,035 (94.0%)
Smoking status					
Current smoker	35,624 (9.8%)	3655 (8.8%)	11,636 (8.7%)	11,592 (9.9%)	8741 (12.6%)
Former smoker	127,025 (35.1%)	12,310 (29.7%)	44,151 (32.9%)	43,414 (36.9%)	27,150 (39.2%)
Never smoker	199,544 (55.1%)	25,460 (61.5%)	78,226 (58.4%)	62,564 (53.2%)	33,294 (48.2%)
Healthy alcohol intake (yes) <sup>b</sup>	181,323 (50.1%)	20,437 (49.3%)	68,369 (51.0%)	59,231 (50.3%)	33,358 (48.2%)
Townsend deprivation index <sup>c</sup>	-1.47 (3.00)	-0.89 (3.22)	-1.60 (2.92)	-1.66 (2.90)	-1.25 (3.11)
Major diseases					
Hypertension <sup>d</sup>	192,362 (53.1%)	18,110 (43.7%)	67,417 (50.3%)	66,283 (56.4%)	40,552 (58.6%)
Coronary heart disease <sup>e</sup>	19,105 (5.3%)	1402 (3.4%)	5476 (4.1%)	6879 (5.9%)	5348 (7.7%)
Diabetes <sup>f</sup>	17,102 (4.7%)	1234 (3.0%)	4674 (3.5%)	5934 (5.1%)	5260 (7.6%)
Years of education (>10 years)	251,628 (69.5%)	32,631 (78.8%)	98,318 (73.4%)	78,016 (66.4%)	42,663 (61.7%)
Sleep duration (h/day)	7.17 (1.07)	7.17 (1.05)	7.17 (1.01)	7.18 (1.07)	7.14 (1.17)
Sleep duration ≤7 h/day	229,489 (63.4%)	26,586 (64.2%)	85,679 (63.9%)	73,471 (62.5%)	43,753 (63.2%)
LPA (h/day)	0.87 ± 1.20	0.92 ± 1.25	0.89 ± 1.23	0.87 ± 1.20	0.77 ± 1.08
MPA (h/day)	0.64 ± 1.03	0.69 ± 1.11	0.67 ± 1.07	0.65 ± 1.03	0.56 ± 0.92
VPA (h/day)	0.21 ± 0.42	0.23 ± 0.43	0.22 ± 0.42	0.21 ± 0.42	0.20 ± 0.41
No MVPA	42,898 (11.8%)	4005 (9.7%)	13,791 (10.3%)	14,406 (12.3%)	10,696 (15.5%)
Regularly taking pain-relief medications <sup>g</sup>	139,439 (38.5%)	13,294 (32.1%)	48,301 (36.0%)	47,450 (40.4%)	30,394 (43.9%)
Regularly taking gastrointestinal agents <sup>h</sup>	15,178 (4.2%)	1410 (3.4%)	5166 (3.9%)	5232 (4.5%)	3370 (4.9%)

<sup>a</sup> Mean values (SD) for continuous variables and n (%) for categorical variables.

<sup>b</sup> Healthy alcohol intake: male: <28 g/day; female: <14 g/day.

<sup>c</sup> This index is a composite score based on 4 key variables: unemployment, overcrowded household, non-car ownership, and non-home ownership.

<sup>d</sup> Hypertension diagnosed by a doctor.

<sup>e</sup> Coronary heart disease diagnosed by a doctor.

<sup>f</sup> Diabetes diagnosed by a doctor.

<sup>g</sup> Taking aspirin, ibuprofen, and/or paracetamol.

<sup>h</sup> Taking ranitidine, omeprazole, and/or laxatives.

Abbreviations: BMI = body mass index; LPA = light physical activity; MPA = moderate physical activity; MVPA = moderate-to-vigorous physical activity; VPA = vigorous physical activity.

**Table 2**  
Associations of SB, PA, and sleep with the odds of IBS in UK Biobank participants.

Activity	n <sub>case</sub> /n	Model 1		Model 2		Model 3	
		Odds ratio (95%CI)	p	Odds ratio (95%CI)	p	Odds ratio (95%CI)	p
<b>LPA</b>	16,805/362,193	0.983 (0.970–0.997)	0.0160	0.978 (0.965–0.992)	0.0017	0.980 (0.966–0.993)	0.0031
<b>MPA</b>	16,805/362,193	0.989 (0.973–1.004)	0.1600	0.985 (0.969–1.001)	0.0600	0.986 (0.971–1.002)	0.0900
<b>VPA</b>	16,805/362,193	0.913 (0.874–0.955)	<0.0001	0.907 (0.868–0.949)	<0.0001	0.921 (0.881–0.962)	0.0002
<b>With MVPA</b>							
Yes	14,552/319,295	Ref		Ref		Ref	
No	2253/42,898	1.154 (1.103–1.209)	<0.0001	1.144 (1.092–1.198)	<0.0001	1.121 (1.070–1.174)	<0.0001
<b>Sleep duration (≤7 h/day)</b>	10,734/229,489	0.872 (0.853–0.891)	<0.0001	0.875 (0.856–0.894)	<0.0001	0.887 (0.868–0.907)	<0.0001
<b>Sleep duration (&gt;7 h/day)</b>	6071/132,704	1.206 (1.165–1.248)	<0.0001	1.194 (1.153–1.236)	<0.0001	1.174 (1.133–1.216)	<0.0001
<b>Sedentary time (continuous)</b>	16,805/362,193	1.036 (1.028–1.044)	<0.0001	1.033 (1.026–1.041)	<0.0001	1.026 (1.019–1.034)	<0.0001
<b>Sedentary time (category)</b>							
<2.0 h/day	1896/41,425	Ref		Ref		Ref	
2.0 to <4.0 h/day	6302/134,013	1.076 (1.021–1.135)	0.0064	1.073 (1.018–1.131)	0.0091	1.056 (1.001–1.113)	0.0470
4.0 to ≤6.0 h/day	5552/117,570	1.194 (1.132–1.261)	<0.0001	1.184 (1.122–1.251)	<0.0001	1.147 (1.086–1.211)	<0.0001
>6.0 h/day	3055/69,185	1.261 (1.188–1.338)	<0.0001	1.244 (1.171–1.322)	<0.0001	1.188 (1.118–1.263)	<0.0001

Notes: Model 1 is adjusted for age, sex, and ethnicity; Model 2 is additionally adjusted for BMI category, smoking status, healthy alcohol intake, and years of education (<10 years or ≥10 years); Model 3 is additionally adjusted for hypertension, coronary heart disease, diabetes, Townsend deprivation index, taking pain-relief medications (yes/no), and taking gastrointestinal agents (yes/no).

Abbreviations: 95%CI = 95% confidence interval; BMI = body mass index; IBS = irritable bowel syndrome; LPA = light physical activity; MPA = moderate physical activity; MVPA = moderate-to-vigorous physical activity; PA = physical activity; Ref = reference; SB = sedentary behavior; VPA = vigorous physical activity.

Table 3

Independent associations of SB, PA, and sleep with incident IBS in UK Biobank participants.

Activity	<i>n<sub>case</sub></i> / <i>n</i>	Model 1		Model 2		Model 3	
		Hazard ratio (95%CI)	<i>p</i>	Hazard ratio (95%CI)	<i>p</i>	Hazard ratio (95%CI)	<i>p</i>
<b>LPA</b>	19,885/345,388	0.920 (0.908–0.933)	<0.0001	0.933 (0.921–0.946)	<0.0001	0.934 (0.922–0.947)	<0.0001
<b>MPA</b>	19,885/345,388	0.940 (0.926–0.955)	<0.0001	0.952 (0.937–0.966)	<0.0001	0.953 (0.939–0.968)	<0.0001
<b>VPA</b>	19,885/345,388	0.869 (0.836–0.903)	<0.0001	0.879 (0.845–0.915)	<0.0001	0.890 (0.856–0.925)	<0.0001
<b>With MVPA</b>							
Yes	17,401/304,743	Ref		Ref		Ref	
No	2484/40,645	1.075 (1.030–1.121)	0.0008	1.104 (1.058–1.152)	<0.0001	1.086 (1.041–1.133)	0.0001
<b>Sleep duration (<math>\leq</math>7 h/day)</b>	13,079/218,755	0.947 (0.927–0.968)	<0.0001	0.925 (0.906–0.945)	<0.0001	0.938 (0.918–0.959)	<0.0001
<b>Sleep duration (<math>&gt;</math>7 h/day)</b>	6806/126,633	1.045 (1.006–1.085)	0.0230	1.072 (1.032–1.114)	0.0003	1.055 (1.016–1.096)	0.0055
<b>Sedentary time (continuous)</b>	19,885/345,388	1.010 (1.003–1.016)	0.0031	1.022 (1.015–1.029)	<0.0001	1.017 (1.010–1.024)	<0.0001
<b>Sedentary time (category)</b>							
<2.0 h/day	2296/39,529	Ref		Ref		Ref	
2.0 to <4.0 h/day	7324/121,771	0.996 (0.951–1.044)	0.8800	1.022 (0.975–1.071)	0.3700	1.015 (0.968–1.064)	0.5400
4.0 to $\leq$ 6.0 h/day	6432/112,018	1.031 (0.983–1.082)	0.2100	1.086 (1.035–1.140)	0.0008	1.066 (1.015–1.119)	0.010
>6.0 h/day	3833/66,130	1.059 (1.005–1.116)	0.0310	1.143 (1.084–1.206)	<0.0001	1.108 (1.050–1.169)	0.0002

Notes: Model 1 is adjusted for age, sex, and ethnicity; Model 2 is additionally adjusted for BMI category, smoking status, healthy alcohol intake, and years of education (<10 years or  $\geq$ 10 years); Model 3 is additionally adjusted for hypertension, coronary heart disease, diabetes, Townsend deprivation index, taking pain-relief medications (yes/no), and taking gastrointestinal agents (yes/no).

Abbreviations: 95%CI = 95% confidence interval; BMI = body mass index; IBS = irritable bowel syndrome; LPA = light physical activity; MPA = moderate physical activity; MVPA = moderate-to-vigorous physical activity; PA = physical activity; Ref = reference; SB = sedentary behavior; VPA = vigorous physical activity.

12.1% (95% confidence interval (95%CI): 1.070–1.174) higher odds of having IBS than those with MVPA; and compared to participants with  $\leq$ 2 h/day of SB, those with excessive SB time had 18.8% (95%CI: 1.118–1.263) higher odds of having IBS.

### 3.3. Associations of SB, PA, and sleep with incident IBS

Among the 345,388 participants who were free of IBS at baseline, 19,885 of them developed IBS during the follow-up. When examined individually, each activity was significantly associated with IBS risk (Table 3). The fully adjusted model

showed that 1 h/day increases in LPA, MPA, and VPA were related to a 6.6% (95%CI: 0.922–0.947), 4.7% (95%CI: 0.939–0.968), and 11.0% (95%CI: 0.856–0.925) lower risk of IBS, respectively. The same increase in SB was associated with a 1.7% (95%CI: 1.010–1.024) higher risk. A 1-h increase in sleep duration showed mixed effects, as seen in U-shaped associations with a 6.2% (95%CI: 0.918–0.959) lower risk of IBS for individuals sleeping  $\leq$ 7 h/day and a 5.5% (95%CI: 1.016–1.096) higher risk for individuals sleeping  $>$ 7 h/day. As shown in Fig. 1, sleep duration demonstrated a U-shaped dose-response relationship with IBS risk, while other

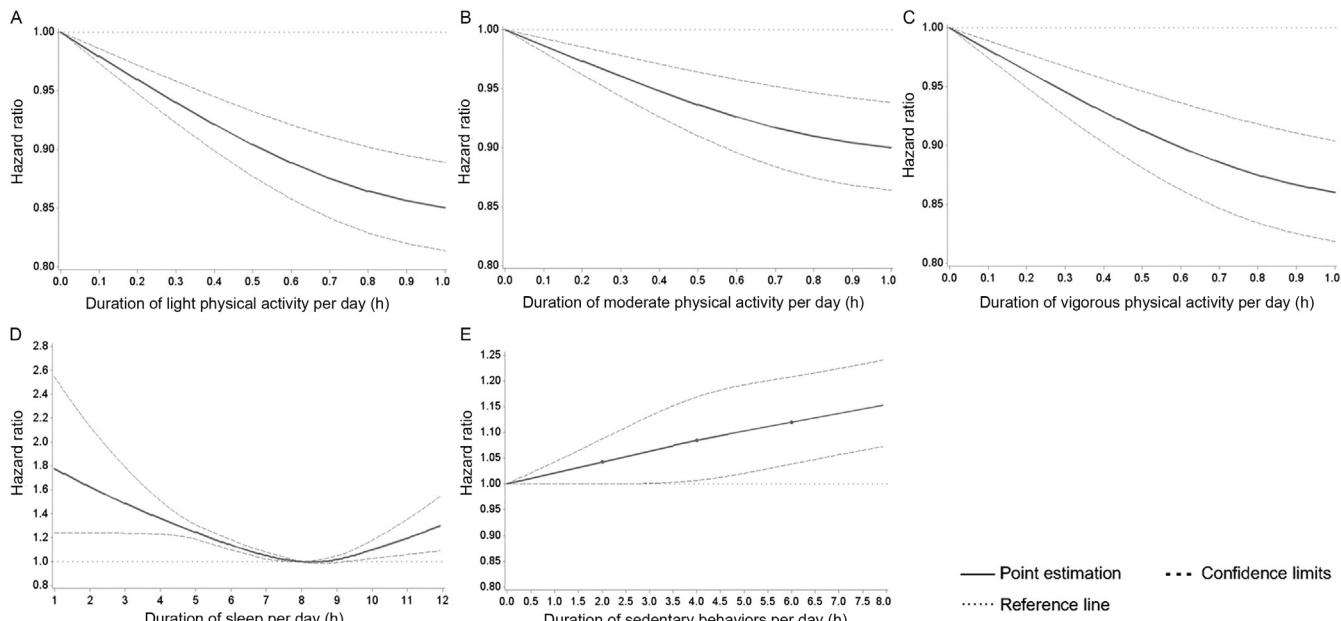


Fig. 1. Graphs of the best-fitting models for independent relationships of physical activity, sleep duration, and sedentary time with incident irritable bowel syndrome.

Table 4

Associations of PA and sleep with incident IBS by replacing SB using isotemporal substitution model in the whole population and subpopulations by sleep duration.<sup>a</sup>

Activity	Hazard ratio (95%CI)	<i>p</i>
<b>Whole population</b>		
LPA	0.929 (0.914–0.944)	<0.0001
MPA	0.978 (0.961–0.996)	0.0190
VPA	0.922 (0.884–0.962)	0.0002
Sleep duration ( $\leq 7$ h/day)	0.905 (0.883–0.929)	<0.0001
Sleep duration ( $> 7$ h/day)	1.031 (0.992–1.071)	0.1500
<b>Sleep duration <math>\leq 7</math> h/day</b>		
LPA	0.919 (0.901–0.937)	<0.0001
MPA	0.982 (0.960–1.005)	0.1200
VPA	0.942 (0.896–0.991)	0.0220
Sleep duration	0.908 (0.885–0.932)	<0.0001
<b>Sleep duration <math>&gt; 7</math> h/day</b>		
LPA	0.952 (0.926–0.978)	0.0005
MPA	0.971 (0.941–1.001)	0.0600
VPA	0.880 (0.815–0.949)	0.0010
Sleep duration	1.030 (0.990–1.072)	0.1500

<sup>a</sup> Model is adjusted for age, sex, ethnicity, BMI category, smoking status, healthy alcohol intake, years of education (<10 years or  $\geq 10$  years), hypertension, coronary heart disease, diabetes, Townsend deprivation index, taking pain-relief medications (yes/no), and taking gastrointestinal agents (yes/no). In the whole population, sleep duration was treated as a piecewise variable with a breakpoint at 7 h ( $\leq 7$  h/day and  $> 7$  h/day).

Abbreviations: 95%CI = 95% confidence interval; BMI = body mass index; IBS = irritable bowel syndrome; LPA = light physical activity; MPA = moderate physical activity; PA = physical activity; SB = sedentary behavior; VPA = vigorous physical activity.

activities demonstrated monotonic increasing (SB) and decreasing (PA) trends.

Partition models mutually adjusting for SB, PA, and sleep showed that neither increasing PA nor keeping sleep duration at 7 h was able to mitigate the adverse effect of SB on IBS development, with an essentially unchanged increased risk of 1.4% (95%CI: 1.007–1.021) (Supplementary Table 2). By the sleep duration category ( $\leq 7$  h/day and  $> 7$  h/day), effects of SB were only slightly attenuated in individuals with shorter sleep duration (hazard ratio (HR) = 1.012, 95%CI: 1.003–1.020). Estimates of sleep duration were essentially unchanged, but estimates of the various PAs were attenuated to different extents in the partition model by sleep duration.

Subsequently, the isotemporal substitution model was conducted to understand the benefits of replacing SB with PA and healthy sleep. In the whole population (Table 4), replacing 1 h of SB with equivalent LPA was associated with an additional 1.3% reduction in IBS risk (HR = 0.929; 95%CI: 0.914–0.944) compared to increasing LPA by 1 h in the partition model (Supplementary Table 2; HR = 0.942; 95%CI: 0.928–0.956). This reduction was also higher than that yielded from the individual model (Table 3; HR = 0.934; 95%CI: 0.922–0.947). Similar reductions in IBS risk were also observed for MPA, VPA, and sleep. As shown in Table 4, Fig. 2, and Supplementary Fig. 2, for individuals without adequate sleep, replacing 1 h of SB with equivalent LPA, VPA, and sleep was associated with an 8.1% (95%CI: 0.901–0.937), 5.8% (95%CI: 0.896–0.991), and 9.2% (95%CI: 0.885–0.932) lower IBS risk,

respectively. For individuals already sleeping  $> 7$  h/day, replacing 1 h of SB with equivalent LPA and VPA were significantly associated with a 4.8% (95%CI: 0.926–0.978) and 12.0% (95%CI: 0.815–0.949) reduction in IBS risk, respectively. Replacement of SB with MPA showed positive but marginal benefit (HR = 0.971; 95%CI: 0.941–1.001). These estimates remained essentially unchanged in the isotemporal substitution model that additionally adjusted for healthy diet and the stress experience over the last 2 years (Supplementary Table 3).

We conducted another 3 sensitivity analyses. When we excluded individuals who had IBS cases occur in the first 2 years of follow-up (Supplementary Table 4), the benefit of replacing SB with equivalent LPA increased slightly, while the benefit of replacing SB with equivalent VPA was reduced. When we excluded those without any MPA or VPA (Supplementary Table 5), the benefits of any PA and healthy sleep were attenuated slightly. For older individuals ( $\geq 60$  years), the benefits of healthy sleep duration dropped considerably compared to younger individuals. LPA and VPA showed better risk reduction in older adults sleeping  $> 7$  h/day, but the differences were not statistically significant (Supplementary Table 6).

### 3.4. Genetic impact on the associations of PA, sleep duration, and sedentary time with incident IBS

Additionally, we tested the interplay between activity and genetic predisposition to IBS by sleep duration in the primary isotemporal substitution model (Table 5). The continuous GRS did not have additional robust impacts on the associations between any activities and IBS risk except for VPA among individuals sleeping  $> 7$  h/day (*p*-interaction = 0.019). Replacement of SB with 1 h VPA was associated with a 6.9% lower IBS risk (HR = 0.931; 95%CI: 0.842–1.029) in individuals with high genetic risk, and the IBS risk reduction more than doubled (17.7% lower IBS risk) in those with low genetic risk (HR = 0.823; 95%CI: 0.733–0.924).

## 4. Discussion

Leveraging a large population-based cohort, our study found that SB was positively associated with higher IBS risk; PA, especially LPA and VPA, could help reduce the risk, and sleeping for a duration of 7 h per day could yield the lowest IBS risk. Although SB and unhealthy sleep duration are risk factors for IBS, replacing SB with LPA or VPA and keeping a healthy sleep duration could mitigate IBS risk regardless of genetic predisposition to IBS. Rather than simply increasing the time of PA or getting adequate sleep, replacing SB with sleep yielded the biggest reduction in IBS risk for people sleeping  $\leq 7$  h/day, but VPA could be the best option to reduce IBS risk for people sleeping  $> 7$  h/day.

To the best of our knowledge, this is the first study addressing the prospective associations of SB, PA, and sleep duration with IBS in a large population. The cross-sectional association between SB and IBS was reported by Vasquez-Rios et al.<sup>9</sup> in 2019, who suggested a sedentary lifestyle may be an independent risk factor for IBS in 346 medical students. A possible mechanism is the incapacity of the human body to

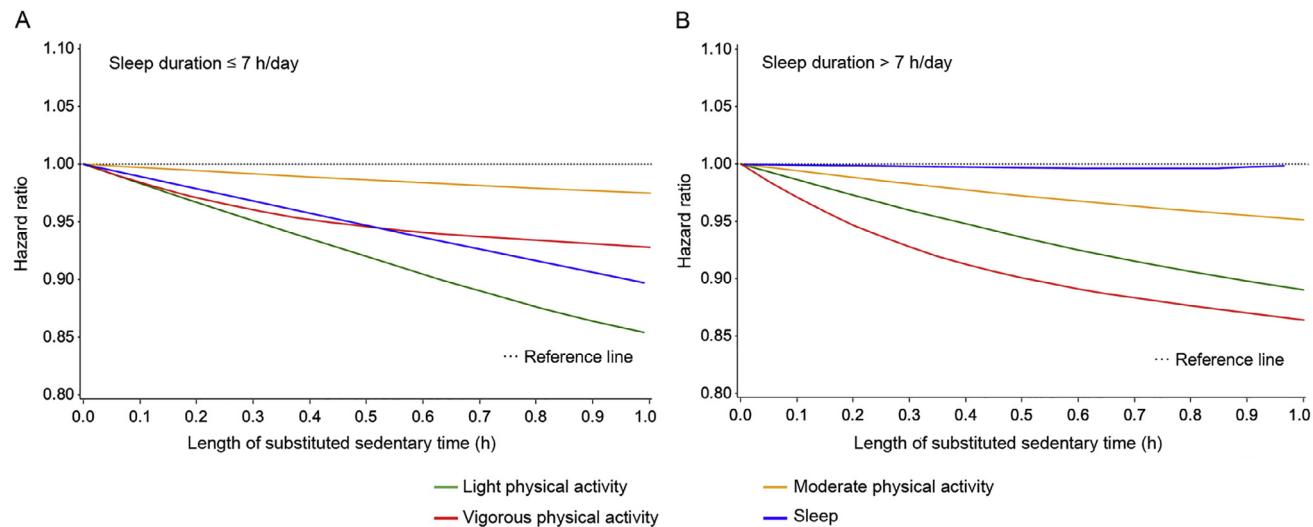


Fig. 2. Best-fitting models for the effect of substituting sedentary time for physical activity or sleep in participants by sleep duration category ((A)  $\leq 7$  h/day and (B)  $> 7$  h/day).

manage the attenuation of the effect of gravitational force that aids descending colon motility. Furthermore, SB could lead to and enhance chronic partial obstruction, potentially causing IBS.<sup>22</sup> Their evidence, like ours, highlights the possibility that PA could mitigate IBS risk. Several randomized controlled trials and a qualitative study seeking physical treatment regimens for IBS patients have been conducted over the past decade.<sup>7,8,23,24</sup> The most recent review of 11 randomized controlled trials with data from 622 participants yielded that PA may improve symptoms but not quality of life or abdominal pain in people diagnosed with IBS.<sup>8</sup> Unfortunately, since the included findings had relatively low certainty, using PA as part of IBS symptom management warrants further evidence. Unlike the moderate improvement associated with PA in IBS patients, our study observed robust reductions in IBS risk when SB is replaced with LPA and VPA. It could be the case that PA helps prevent IBS, but more solid clues from

randomized controlled trials or other experimental studies are needed to validate this finding.

Sleep duration of 7–8 h per day is reported to be an essential element of a healthy lifestyle, potentially reducing the mortality risks of all-cause, cardiovascular diseases, and cancer, as well as the risks of major chronic diseases.<sup>19,25</sup> In agreement with a previous review,<sup>12</sup> we found that abnormal sleep duration was associated with IBS at baseline. Many studies have shown the adverse effects of poor sleep in IBS patients, with exacerbated IBS symptoms after experiencing poor sleep.<sup>5,12</sup> Our study further highlighted that in IBS-free individuals, maintaining a healthy sleep pattern could lower the future risk of IBS, which moreover indicates the bidirectional relationship between sleep and IBS. Sleep quality is also related to mood disorders, including depression and anxiety,<sup>26</sup> both of which are much more frequent in IBS patients.<sup>5</sup> This has been underlined by the dysfunction within the bidirectional gut–brain axis, which is

Table 5  
Associations of PA and sleep with incident IBS by replacing SB using isothermal substitution model in subpopulations with high/low genetic risks by sleep duration.<sup>a</sup>

Activity	Low genetic risk		High genetic risk		Interaction $p^b$
	Hazard ratio (95%CI)	$p$	Hazard ratio (95%CI)	$p$	
<b>Sleep duration <math>\leq 7</math> h/day</b>					
LPA	0.915 (0.889–0.941)	<0.0001	0.923 (0.897–0.949)	<0.0001	0.7600
MPA	0.986 (0.955–1.019)	0.4000	0.978 (0.947–1.010)	0.1700	0.6400
VPA	0.969 (0.904–1.039)	0.3800	0.915 (0.851–0.985)	0.0190	0.2800
Sleep duration	0.896 (0.864–0.929)	<0.0001	0.922 (0.888–0.956)	<0.0001	0.1900
<b>Sleep duration <math>&gt; 7</math> h/day</b>					
LPA	0.948 (0.910–0.988)	0.0110	0.954 (0.919–0.991)	0.0150	0.1200
MPA	0.978 (0.934–1.024)	0.3400	0.964 (0.924–1.006)	0.0900	0.1700
VPA	0.823 (0.733–0.924)	0.0010	0.931 (0.842–1.029)	0.1600	<b>0.0190</b>
Sleep duration	1.032 (0.991–1.025)	0.2800	1.028 (0.972–1.088)	0.3300	0.7500

<sup>a</sup> Model is adjusted for age, sex, ethnicity, BMI category, smoking status, healthy alcohol intake, years of education (<10 years or  $\geq 10$  years), hypertension, coronary heart disease, diabetes, Townsend deprivation index, taking pain-relief medications (yes/no), and taking gastrointestinal agents (yes/no).

<sup>b</sup> Tested in models with the interaction terms of continuous genetic risk score and corresponding activities.

Abbreviations: 95%CI = 95% confidence interval; BMI = body mass index; IBS = irritable bowel syndrome; LPA = light physical activity; MPA = moderate physical activity; PA = physical activity; SB = sedentary behavior; VPA = vigorous physical activity.

thought to play a key role in the genesis and maintenance of symptoms in IBS.<sup>27</sup> In line with this, our GRS was constructed based on 6 SNPs sharing genetic pathways with mood and anxiety disorders.<sup>14</sup> However, this genetic background only moderately modified the association between VPA and IBS risk for participants sleeping >7 h/day. This could be plausible due to the moderate IBS genome-wide SNP heritability,<sup>14</sup> which may infer that neuronal pathways play a limited role in the progression of IBS, while behavioral factors are potentially at work via other underlying biological pathways.

Sleep and PA are not independent activities but may interact with each other. Although debate exists, studies have found that sleep duration and PA are bidirectionally linked with limited effects.<sup>28,29</sup> Many PA-related studies combine MPA and VPA into MVPA when elucidating the health benefits of PA. In our study, VPA outperformed MPA in terms of IBS risk reduction, especially in individuals with adequate sleep. This may be partially explained by the findings of a previous systematic review,<sup>28</sup> which showed that VPA was associated with better sleep quality in older adults; our sensitivity analysis by age group confirmed this as well. The benefit of replacing SB with VPA may be boosted further by adequate sleep duration. Altogether, evidence implies that further studies are needed to explore detailed exercise suggestions according to age group.

This study has several strengths, including the large sample size, detailed records of intestinal system status and daily behaviors, and phenotype data available on a wide range of potential covariates and genetic variants allowing for the evaluation of gene and environment interaction. Several limitations should be noted as well when interpreting the results. First, as a volunteer cohort, participants in the UK Biobank do not represent the UK population—they tend to be healthier and wealthier.<sup>30,31</sup> Such individuals may have lower IBS risk and be relatively in better health overall. Second, our IBS identification was according to the ICD-10 codes, which shifted from Rome III to Rome IV during the follow-up. Furthermore, our ancillary online questionnaires were only conducted for ~1/3 of the participants. These inconsistencies could lead to misclassification of incident IBS cases and, therefore, to the underestimation of IBS risk in our cohort. Misclassification could distort our findings towards null; our effect-size estimates are therefore conservative. Third, we could not further examine the associations of the activities with different IBS subtypes because of the unavailability of data. Future long-term studies are needed to elucidate whether replacing SB with PA or healthy sleep duration is applicable for reducing the risks of different IBS subtypes. Also, the activity measurement of the UK Biobank did not include other domains like occupation, transportation, and household, and the durations and frequencies were based on self-reported questionnaires. Self-report bias and missing information may compromise the statistical power of the model to detect the differences in IBS risk. For sleep duration, we used the 4-week averaged daily sleep duration to minimize variation, but since people could have various sleep durations over their lifetime and we did not have the data on sleep quality (including but not restricted to

sleep latency and sleep efficiency, which could not be yielded from self-reported questionnaires), our sleep duration results ought to be interpreted with caution. Additionally, although we controlled for several factors that could confound our findings, including diet, alcohol, and stress, other risk factors, such as adverse childhood experiences and experience of natural diseases, domestic violence, and bullying were not considered due to lack of data availability. Finally, our participants mostly did not have excessive PA like athletes do. Excessive PA might compromise individuals' health status by inducing psycho-physical stress and affecting the balance of intestinal microbiota, which may interfere with the stability of the intestinal system and thereby promote IBS development.<sup>32</sup>

## 5. Conclusion

Our study investigated the relationships of SB, PA, and sleep with IBS risk in ~0.36 million people, making it one of the largest cohort studies on the subject. Replacing SB with PA and healthy sleep duration could robustly attenuate IBS risk regardless of genetic background. Still, the underlying pathogenesis of IBS is complex, and biological molecular pathophysiology is far from understood. That, along with the paucity of biomarkers and treatments to cure this multifactorial health disorder, warrant future investigations employing larger cohorts and precision measures of activities with wearable monitors or accelerometers to feature the full landscape of the role of healthy behaviors, including regular exercise and high-quality sleep, in IBS prevention.

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## Authors' contributions

XG conceptualized the study, conducted the data cleaning, analyses, and drafted, and reviewed the manuscript; ST coordinated the data collection, and reviewed and revised the manuscript; NH estimated the genetic risk score; GS critically reviewed and revised the manuscript; TH coordinated and supervised the data collection, and reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

## Competing interests

The authors declare that they have no competing interests.

## Supplementary materials

Supplementary materials associated with this article can be found in the online version at [doi:10.1016/j.jshs.2023.02.002](https://doi.org/10.1016/j.jshs.2023.02.002).

## References

1. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. *Nat Rev Dis Primers* 2016;2:16014. doi:10.1038/nrdp.2016.14.
2. Black CJ, Drossman DA, Talley NJ, Ruddy J, Ford AC. Functional gastrointestinal disorders: Advances in understanding and management. *The Lancet* 2020;396:1664–74.
3. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome foundation global study. *Gastroenterology* 2021;160:99–114.
4. National Collaborating Centre for Nursing and Supportive Care (UK). *Irritable bowel syndrome in adults: Diagnosis and management of irritable bowel syndrome in primary care*. London: Royal College of Nursing (UK); 2008.
5. Shiha MG, Aziz I. Review article: Physical and psychological comorbidities associated with irritable bowel syndrome. *Aliment Pharmacol Ther* 2021;54(Suppl. 1):S12–23.
6. Rawla P, Sunkara T, Raj JP. Updated review of current pharmacological and non-pharmacological management of irritable bowel syndrome. *Life Sci* 2018;212:176–81.
7. Johannesson E, Jakobsson Ung E, Ringstrom G, Sadik R. The experiences of physical activity in irritable bowel syndrome—A qualitative study. *J Clin Nurs* 2019;28:3189–99.
8. Nunan D, Cai T, Gardener AD, et al. Physical activity for treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2022;6:CD011497. doi:10.1002/14651858.CD011497.pub2.
9. Vasquez-Rios G, Machicado JD, Tisce R, et al. Stress and a sedentary lifestyle are associated with irritable bowel syndrome in medical students from Peru: A cross-sectional study. *Eur J Gastroenterol Hepatol* 2019;31:1322–7.
10. Sadeghian M, Sadeghi O, Hassanzadeh Keshteli A, Daghaghzadeh H, Esmaillzadeh A, Adibi P. Physical activity in relation to irritable bowel syndrome among Iranian adults. *PLoS One* 2018;13:e0205806. doi:10.1371/journal.pone.0205806.
11. Aufieri MC, Morimoto JM, Viebig RF. Severity of irritable bowel syndrome symptoms and fodmaps intake in university students. *Arg Gastroenterol* 2021;58:461–7.
12. Tu Q, Heitkemper MM, Jarrett ME, Buchanan DT. Sleep disturbances in irritable bowel syndrome: A systematic review. *Neurogastroenterol Motil* 2017. doi:10.1111/nmo.12946.
13. Mekary RA, Ding EL. Isotemporal substitution as the gold standard model for physical activity epidemiology: Why it is the most appropriate for activity time research. *Int J Environ Res Public Health* 2019;16:797. doi:10.3390/ijerph16050797.
14. Eijsbouts C, Zheng T, Kennedy NA, et al. Genome-wide analysis of 53,400 people with irritable bowel syndrome highlights shared genetic pathways with mood and anxiety disorders. *Nat Genet* 2021;53:1543–52.
15. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015;12:e1001779. doi:10.1371/journal.pmed.1001779.
16. Lacy BE, Pimentel M, Brenner DM, et al. ACG clinical guideline: Management of irritable bowel syndrome. *Am J Gastroenterol* 2021;116:17–44.
17. World Health Organization (WHO). *WHO guidelines on physical activity and sedentary behaviour*. Geneva: World Health Organization; 2020.
18. Stamatakis E, Rogers K, Ding D, et al. All-cause mortality effects of replacing sedentary time with physical activity and sleeping using an isotemporal substitution model: A prospective study of 201,129 mid-aged and older adults. *Int J Behav Nutr Phys Act* 2015;12:121. doi:10.1186/s12966-015-0280-7.
19. Huang BH, Duncan MJ, Cistulli PA, Nassar N, Hamer M, Stamatakis E. Sleep and physical activity in relation to all-cause, cardiovascular disease and cancer mortality risk. *Br J Sports Med* 2022;56:718–24.
20. Mekary RA, Willett WC, Hu FB, Ding EL. Isotemporal substitution paradigm for physical activity epidemiology and weight change. *Am J Epidemiol* 2009;170:519–27.
21. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med* 2010;29:1037–57.
22. Robbins SE. A common cause of irritable bowel syndrome and diverticulitis: Chronic distal colon distention from sedentary behavior and excessive dietary fiber. *Expert Rev Gastroenterol Hepatol* 2013;7:413–9.
23. Zhou C, Zhao E, Li Y, Jia Y, Li F. Exercise therapy of patients with irritable bowel syndrome: A systematic review of randomized controlled trials. *Neurogastroenterol Motil* 2019;31:e13461. doi:10.1111/nmo.13461.
24. Johannesson E, Simren M, Strid H, Bajor A, Sadik R. Physical activity improves symptoms in irritable bowel syndrome: A randomized controlled trial. *Am J Gastroenterol* 2011;106:915–22.
25. Covassin N, Singh P. Sleep duration and cardiovascular disease risk: Epidemiologic and experimental evidence. *Sleep Med Clin* 2016;11:81–9.
26. Alvaro PK, Roberts RM, Harris JK. A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. *Sleep* 2013;36:1059–68.
27. Orr WC, Fass R, Sundaram SS, Scheimann AO. The effect of sleep on gastrointestinal functioning in common digestive diseases. *Lancet Gastroenterol Hepatol* 2020;5:616–24.
28. Wang F, Boros S. The effect of physical activity on sleep quality: A systematic review. *Eur J Physiotherapy* 2021;23:11–8.
29. Pesonen AK, Kahn M, Kuula L, et al. Sleep and physical activity—The dynamics of bi-directional influences over a fortnight. *BMC Public Health* 2022;22:1160. doi:10.1186/s12889-022-13586-y.
30. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol* 2017;186:1026–34.
31. Keyes KM, Westreich D. UK Biobank, big data, and the consequences of non-representativeness. *The Lancet* 2019;393:1297. doi:10.1016/S0140-6736(18)33067-8.
32. Wegierska AE, Charitos IA, Topi S, Potenza MA, Montagnani M, Santacroce L. The connection between physical exercise and gut microbiota: Implications for competitive sports athletes. *Sports Med* 2022;52:2355–69.