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Exercise and incidence of myocardial infarction, stroke, hypertension, type 2 diabetes and site-specific cancers

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Title: Exercise and incidence of myocardial infarction, stroke, hypertension, type 2 diabetes

and site-specific cancers

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Abstract

Objective: Little is known about the dose-response relationships between exercise and noncommunicable diseases in East Asians. The objective of this study was to examine longitudinal associations of exercise frequency with the incidence of myocardial infarction, stroke, hypertension, type 2 diabetes and 10 different cancer outcomes.

Design: A prospective cohort study.

Setting: Physical examination data linked with the entire Korean population's health insurance system.

Participants: 257,854 Korean adults who provided up to 7 repeat-measures of exercise and confounders.

Primary outcome measures: Each disease incidence was defined using both fatal and nonfatal health records (a median follow-up period of 13 years).

Results: Compared with no exercise category, the middle categories of exercise frequency (1-2, 3-4 or 5-6 times/week) showed the lowest risk of myocardial infarction (hazard ratio[HR]: 0.79; 95% confidence interval[CI]: 0.70-0.90), stroke (HR: 0.80; 95%CI: 0.73-0.89), hypertension (HR: 0.86; 95%CI: 0.85-0.88), type 2 diabetes (HR: 0.87; 95%CI: 0.84-0.89), stomach (HR: 0.87; 95%CI: 0.79-0.96), lung (HR: 0.80; 95%CI: 0.71-0.91), liver (HR: 0.85; 95%CI: 0.75-0.98) and head & neck cancer (HR: 0.76; 95%CI: 0.63-0.93), exhibiting J-shaped associations. There was, in general, little evidence of effect modification by body mass index, smoking, alcohol consumption, family history of disease, and sex in these associations.

Conclusions: Moderate levels of exercise showed the lowest risk of myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancer. Public health and lifestyle interventions should promote moderate levels of exercise as a behavioral prevention strategy for non-communicable diseases in a wider population of East Asians.

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Article Summary

Strengths and limitations of this study

- This study is the first to investigate the longitudinal associations of exercise with various cardiovascular and cancer incident outcomes in an East Asian population.
- Another strength is the use of a large-scale cohort dataset of adults (n=257,854) who
 provided up to 7 repeated measures of exercise frequency and all confounders in
 order to minimize the risk of regression dilution.
- A limitation is that no strong inference can be drawn about the exercise-incident disease relationships.

Introduction

Prevention and control of non-communicable diseases is a contemporary global public health priority. At present, 40 million deaths per year, which accounts for nearly 70% of total deaths globally, are attributable to non-communicable diseases.^{1,2} Moreover, the number of deaths due to non-communicable diseases, such as cardiovascular disease,³ hypertension,⁴ diabetes⁵ and cancer,⁶ has increased dramatically over the past few decades, although agestandardized cardiovascular disease and cancer rates as well as systolic blood pressure levels⁷ have declined.^{8,9} However, trends in these disease traits have varied across different populations, particularly with less favorable changes observed in East Asian populations compared with Western populations. For example, diabetes rates¹⁰ have increased more rapidly, while age-standardized cardiovascular disease rates³ and systolic blood pressure levels⁷ have fallen less steeply in East Asians in comparison with Westerners.

In addition, adults in East Asia tend to have higher prevalence of physical inactivity,¹¹ which is one of the four target behaviors (including unhealthy diet, tobacco use and harmful use of alcohol) that have been set as the global focus to reduce the risk of non-communicable diseases.¹² The beneficial impacts of increased physical activity on various non-communicable outcomes have been demonstrated by numerous previous investigations. However, the majority of previous research has been predicated on evidence from Western populations, thereby limiting its application to other populations including East Asians. As such, little is currently known about levels of physical activity including exercise in relation to non-communicable diseases in East Asian populations as compared with Western populations.¹³ Another critical gap in the existing literature is the use of data measured only at a single point in time (i.e. baseline), in which case physical activity or exercise levels are assumed to remain constant over time. This methodology, therefore, does not allow for the fact that individuals' physical activity or exercise levels change with time, and hence may increase the potential for regression dilution.¹⁴ Furthermore, it is well-known that temporal changes occur in other traditional behavioral and metabolic risk factors for non-

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communicable diseases, such as adiposity levels,^{15,16} smoking,¹⁷ glucose levels¹⁸ and total cholesterol levels,¹⁹ showing different patterns of changes between East Asian and Western populations. Nevertheless, no previous research of East Asians or Westerners took into account changes in these risk markers in understanding the relationships between physical activity and non-communicable diseases. Moreover, the dose-response relationship between physical activity and various non-communicable disease outcomes has remained unclear in East Asians. Therefore, the purpose of this research was to explore the dose-response relationships between exercise frequency and various types of incident non-communicable diseases, such as myocardial infarction, stroke, hypertension, type 2 diabetes and site-specific cancers, using a large-scale prospective cohort of Korean adults with multiple repeated measures of exercise frequency and other risk markers.

Methods

Study design and participants

This study is based on data from the National Health Insurance Service - Health Screening (NHIS-HEALS) cohort dataset,²⁰ which is a nationally representative random sample (stratified by sex, age, employment status and income) of >500,000 South Korean adults aged 40-79 years between 2002 and 2003 made available by the NHIS. The NHIS is a single health insurance system in South Korea, which manages and maintains information on the entire South Korean population's healthcare utilization; it is mandatory for all South Koreans to take part in the national health insurance system. The NHIS is also responsible for maintaining national health examination programs involving data from general health examinations of all insured employees or self-employed individuals aged >40 years; it is recommended for them to perform the health examination at least every two years. The health examination involves collection of information on body composition, blood profiles, blood pressure, self-reported lifestyles, self-reported physician-diagnosed disease, and self-reported family history of disease.

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The NHIS-HEALS cohort includes a wide variety of information collected between 2002 and 2015: health examination data and demographic and eligibility data (e.g., in-patient and outpatient hospital records, medical bill, health insurance and medical aid beneficiaries, etc.). In the present analysis, we utilized health examination data collected between 2002 and 2008 to define the exercise frequency and all confounders. There was a change in the type of self-report methods in 2009; hence, health examination data collected in or after 2009 were not considered in the analysis due to the inability to harmonize variables. However, we used full follow-up data accrued from 2002 until 2015. This research was approved by the Institutional Review Board (4-2017-0051) of the Yonsei University's Severance Hospital in Republic of Korea.

Exposure

The primary exposure variable of this study was exercise frequency, assessed using questionnaires administered during the health examinations. The specific question asked was "How many times per week do you engage in exercise that causes sweating?" Participants were asked to choose only one of the following 5 possible answers: None, 1-2 times/week, 3-4 times/week, 5-6 times/week and almost every day.

Outcomes

We evaluated 17 different incident disease outcomes in the present study: myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, colon, rectum, lung, liver, head & neck, pancreas, kidney, gallbladder and esophagus cancer. Participants' in-patient and outpatient hospital records (i.e. non-fatal status) and death records (i.e. fatal status) obtained through linkage with Statistics Korea were both classified according to the International Classification of Disease (ICD)-10 codes to classify different incidence types (Supplementary Table 1). Additionally, blood pressure (e.g., systolic \geq 140 mmHg, diastolic \geq 90 mmHg) and fasting glucose levels (e.g., \geq 126 mg/dL), both of which were measured during physical examinations, were used in conjunction with physician diagnosis information and ICD-10

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codes to define incident hypertension and type 2 diabetes, respectively. Each incident disease outcome was defined as the first occurrence of either non-fatal or fatal respective disease cases. Follow-up was censored at occurrence of an incident disease outcome or the end date of hospital and death records (December 31st, 2015). The median follow-up was 13.0 years (interquartile range: 10.2-11.3 years)

Confounders

The following variables were included as confounders in the analyses: sex, body mass index, systolic blood pressure, fasting glucose, total cholesterol, family history of heart disease, stroke or hypertension [only in models for incident myocardial infarction, stroke or hypertension], family history of diabetes [only in models for type 2 diabetes], family history of cancer [only in models for incident cancer outcomes], smoking status (never, previously, currently) and alcohol consumption (never, 2-3 times/month, 1-2 times/week, ≥3 times/week).

Statistical analysis

Cox regression with age as the underlying time scale was used to estimate the associations of exercise frequency with each incident disease outcome, with adjustment for all the abovementioned confounders as well as without any adjustment. Data were structured to enable the inclusion of exercise frequency and all confounders from both baseline and up to 6 repeated measures as time-updated covariates. This approach takes into account changes in exercise frequency as well as each confounder over time in relation to disease incidence. Individuals who reported no exercise served as a reference group for all comparisons. Effect modification by body mass index (<25, ≥ 25 kg²/m), smoking status, alcohol consumption, family history of disease and sex was also examined for each incident disease outcome. Visual inspections of log-log plots provided support for the assumptions of proportional hazards for all covariates. A sensitivity analysis where incident disease cases occurring during the first 2 years of follow-up were removed was performed to address reverse

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causality. Analyses were performed in Stata/SE Version 14 (StataCorp LP, College Station,

Patient and Public Involvement.

TX).

Neither patients nor members of the public were involved in this study.

Results

Of an initial sample of 512,190 individuals, 74,931 had missing data on at least one of the model covariates, and 179,405 had self-reported physician-diagnosed heart attack, stroke, hypertension (additionally, systolic \geq 140 mmHg or diastolic \geq 90 mmHg), diabetes (additionally, fasting glucose levels \geq 126 mg/dL) or cancer at baseline, respectively. Excluding these individuals resulted in a final sample for analysis of 257,854 individuals (Figure 1).

Individuals provided up to 7 measures of exercise frequency and each confounder (i.e. baseline plus 6 repeated measures). Participants' characteristics at baseline are summarized in Table 1. Supplementary Table 2 summarizes participants' characteristics at each repeat assessment. Individuals in the categories of 1-2, 3-4 or 5-6 times/week of exercise were slightly younger, but showed higher proportions of family history of disease and lower proportions of never smoking or drinking alcohol, compared with those in the categories of none or almost every day of exercise. Across the seven time points (Supplementary Figure 2), the proportion of individuals who reported no exercise decreased while the proportion who reported 1-2 or 3-4 times/week of exercise increased; there were no noticeable changes for the categories of 5-6 times/week or almost every day of exercise. Overall, J-shaped associations were found between exercise frequency and incident myocardial infarction, stroke, hypertension and type 2 diabetes. Hazard ratios for these diseases were lowest in the middle categories of exercise frequency (e.g., 3-4 or 5-6 times/week) (Figure 2). There were no associations for the most frequent exercise category

(e.g., almost every day) with the incidence of myocardial infarction, stroke and type 2 diabetes.

J-shaped associations were also found for incident stomach, lung, liver and head & neck cancer (Figure 3). Higher exercise frequencies (e.g., 1-2, 3-4 times/week and almost every day) were associated with lower hazards of incident stomach cancer. No statistical significance was observed for incident colon, rectum, pancreas, kidney, gallbladder and esophagus cancer. Crude event rates per 100,000 person-years in the middle categories of exercise frequency were relatively lower for incident rectum, and esophagus cancer, but higher for incident pancreas, kidney and gallbladder cancer. Cox regression models with no adjustment for confounders (Supplementary Figure 2) and a sensitivity analysis (Supplementary Figure 3) in which incident cases occurring in the first 2 years of follow-up were removed both revealed nearly identical patterns of associations as the main analyses. Figure 4 shows comparisons of results that showed statistical significance for multiplicative interaction terms between exercise frequency and each incident disease outcome. Strong Jshaped associations for incident hypertension were identified at each level of body mass index. J-shaped associations of exercise frequency with incident hypertension were strong only in the more favorable levels of smoking (e.g., never, previously) and alcohol consumption (e.g., never, 2-3times/month, 1-2times/week); no or weak associations were identified in the most harmful level of smoking (e.g., current smokers) and alcohol consumption (e.g., ≥3times/week). J-shaped associations were evident at all levels of family history of CVD and sex for incident hypertension, and sex for incident type 2 diabetes. Exercise frequency was associated with incident lung cancer in non-obese individuals, but there was no evidence of association in obese individuals. All comparisons stratified by each potential effect modifier are presented in Supplementary Figures 4 and 5.

Discussion

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This is the first investigation examining the prospective associations of exercise with various incident non-communicable disease outcomes using multiple repeated measures of covariates in East Asian populations. We identified J-shaped associations of exercise frequency with incident myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancer, with the greatest benefits being observed in the middle categories of exercise frequency (e.g., 1-2, 3-4 or 5-6 times/week). These findings provide two important clinical and public health implications. First, prevention and management of non-communicable diseases in East Asians may benefit considerably from employing an exercise promotion approach in the context of combined non-communicable disease prevention. Mechanism research indicates that cardiovascular disease and type 2 diabetes have similar biological pathways relating to exercise,^{21,22} so an integrated prevention approach can be applied to control and manage these two diseases at a minimum.⁵ Moreover, regular participation in exercise can induce favorable changes in intermediate cardiometabolic risk markers,²³ which are important predictors of typical non-communicable diseases. Hence, promoting exercise has great potential to act as an integrative behavioral strategy for preventing and controlling various non-communicable diseases simultaneously in East Asian populations.

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Second, individuals who engage in exercise 1-2, 3-4 or 5-6 times/week, rather than every day, may be able to reduce their risk of developing myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancer. Similar J-shaped associations between high intensity exercise (e.g., running) and cardiovascular disease risk have also been reported in previous cohort studies of Western^{24,25} and Japanese adults.²⁶ Nevertheless, the present study as well as previous research²⁴⁻²⁶ found that the risk of developing cardiovascular events in individuals who had the highest level of exercise was not noticeably higher compared with those who had the lowest level of exercise. No previous research in East Asians has found such J-shaped relationships between exercise or physical activity and other incident disease outcomes such as hypertension,²⁷⁻³¹ diabetes³²⁻³⁹ and different type of cancers.⁴⁰⁻⁴⁶ However, previous meta-

analyses of cohort studies comprising predominantly Westerners found leisure-time physical activity to have curvilinear (but not J-shaped) associations with the incidence of type 2 diabetes,⁴⁷ and linear associations with the incidence of hypertension⁴⁸ and various site-specific cancers (liver, lung, head & neck, kidney, colon, rectal, bladder, gastric cardia, breast, endometrial, myeloid leukemia, myeloma, esophageal adenocarcinoma).⁴⁹ While additional research is needed to confirm the J-shaped associations of exercise with various incident diseases in other samples of East Asians, findings of this research provide a strong rationale for development and implementation of public health policies and clinical trials aimed at promoting a moderate level of exercise to minimize the risk of myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancer.

Another finding of this research is that associations of exercise frequency with hypertension were modified by body mass index, smoking, alcohol consumption, family history of cardiovascular disease and sex: lung cancer by body mass index and type 2 diabetes by sex. Notably, exercise frequency was not associated with hypertension in individuals who are smokers or drinking alcohol ≥3 times/week (except for 3-4 times/week of exercise). This observation provides some evidence that the harmful impacts of smoking or binge drinking on hypertension⁵⁰⁻⁵² may not be offset completely by exercise. This, in turn, appears to advocate for the need for implementing a combined hypertension prevention strategy targeting promotion of exercise in conjunction with smoking cessation and reductions in alcohol consumption in East Asians.¹³ For lung cancer, the null associations in individuals with body mass index \geq 25 may be indicative of potential residual confounding through reported bias in smoking behaviors. Nonetheless, there was little evidence for effect modification for other disease comparisons, highlighting the importance of promoting exercise for the prevention of various non-communicable diseases in individuals at different categories of body mass index, smoking, alcohol consumption, family history of disease and sex.

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This study has several notable strengths. First, we used data from a large prospective cohort study in which exercise and other risk markers were assessed on multiple occasions (up to 7 times). Nearly 84% and 5% of the full participants provided 1 and 6 repeated measures of all covariates, respectively. Compelling evidence indicates that the risk of regression dilution can be reduced using repeated measures of exposure and confounders.¹⁴ Moreover, we examined the dose-response-relationship of exercise frequency with a wide variety of specific types of incident non-communicable disease outcomes simultaneously using inpatient and out-patient diagnosis data as well as mortality data. The large sample size (n=257,854) is another strength.

This study has some limitations. Findings of this study may not be generalizable to adult populations of other countries. Due to the observational nature of this research, no strong inference can be drawn about the exercise-incident disease relationships. In addition, the accuracy of hospital admission records is uncertain, although the accuracy of death records from Statistics Korea was found to be 92% in previous research.⁵³ No information about medication use was available in the cohort data, so we could not use it as a potential confounder and another condition when defining disease status (e.g., hypertension, type 2 diabetes) at both baseline and follow-up. Furthermore, no exercise duration was assessed; hence, inference was made purely based on exercise frequency. Moreover, ICD-10 codes for sex-specific cancers (e.g., prostate and breast cancer) were masked due to the data management policy set forth by the NHIS, so it was not possible to examine such cancers in the present study. The lack of data on diet, which is another behavioral risk marker for non-communicable diseases¹² is another limitation.

Conclusion

Exercise frequency showed J-shaped associations with the risk of developing myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancer, with the lowest risks found in individuals who engaged in exercise 1-2, 3-4 or 5-6 times/week as opposed to every day. These findings were generally applicable to different

sub-populations as stratified by body mass index, smoking, alcohol consumption, family history of disease, and sex. Public health and lifestyle interventions should promote a moderate level of exercise as a behavioral strategy for prevention and control of noncommunicable diseases in a wider population of East Asians.

Author Contributions

YK designed this study, performed statistical analysis, and drafted an initial version of the manuscript. SJS, SMH and SHJ all contributed to conceptualizing the study idea and developing the analytical plans, and provided assistance with statistical analysis. All authors critically reviewed, approved of the final version of the manuscript, and agreed to be responsible for all facets of this work.

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Conflicts of interest

None declared.

Patient consent

Not required.

Ethics approval

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This research was approved by the Institutional Review Board (4-2017-0051) of the Yonsei University's Severance Hospital in Republic of Korea.

Data sharing statement

Data sharing is not applicable because no informed consent for data sharing was obtained from the participants.

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Figure Legends

Figure 1. A flow diagram. Note: "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data without missingness and prevalence of major diseases were used to create final analysis datasets for different incident disease outcomes; while the number of unique participants at baseline is the same for all incident disease outcomes, the total number of observations varied due to the nature of time-updated covariate analyses (i.e. censoring of subsequent time-updated covariates when an incident

 disease case occurs before the end date of repeated measures). Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million Korean adults (2002-2015) with the entire Korean population's health insurance system.

Figure 2. Associations of exercise frequency with various incident cardiovascular disease outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of heart disease, stroke or hypertension (in models for myocardial infarction, stroke and hypertension) or diabetes (in models for Type 2 diabetes), smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million Korean adults (2002-2015) with the entire Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

Figure 3. Associations of exercise frequency with various incident cancer outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of cancer, smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million Korean adults (2002-2015) with the entire Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

Figure 4. Results from assessment of effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequency and each incident disease outcome. Only associations for which the multiplicative interaction terms were statistically significant are presented. Cox regression models with age as the underlying timescale were adjusted for sex [not in models for effect modification by sex], body mass index [not in models for effect modification by body mass index], systolic blood pressure, fasting glucose levels, total cholesterol levels, family history [not in models history of respective disease heart for effect modification bv familv of disease/stroke/hypertension (in models for myocardial infarction, stroke and hypertension), diabetes (in models for Type 2 diabetes) or cancer (in models for each cancer), smoking status [not in models for effect modification by smoking status] and alcohol consumption [not in models for effect modification by alcohol consumption]. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. P-values for multiplicative interactions with exercise frequency are as follows; Outcome - hypertension: body mass index (0.049), smoking (<0.001), alcohol consumption (<0.001), family history of cardiovascular disease (0.029) and sex (<0.001); Outcome - lung cancer: body mass index (0.016), and; Outcome - type 2 diabetes: sex (0.012). Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million Korean adults (2002-2015) with the entire Korean population's health insurance system. Abbreviations: HR -Hazard Ratio; CI - Confidence Intervals

Table 1. Characteristics of the participants at baseline.

Variables	All (n=257,854)	Exercise frequency					
		None (n=148,284)	1-2 times/week (n=62,923)	3-4 times/week (n=24,836)	5-6 times/week (n=6,676)	Almost everyda (n=15,135)	
Sex, %							
Men	50.5%	43.8%	63.3%	57.5%	52.9%	49.6%	
Women	49.5%	56.2%	36.7%	42.5%	47.1%	50.4%	
Age, years	50.7 (8.7)	51.5 (9.2)	49.0 (7.5)	49.3 (7.5)	49.9 (7.8)	53.5 (9.3)	
Body Mass Index, kg ² /m	23.5 (2.8)	23.3 (2.9)	23.6 (2.7)	23.7 (2.6)	23.7 (2.6)	23.7 (2.7)	
Systolic blood pressure, mmHg	116.8 (11.2)	116.6 (11.3)	117.1 (11.0)	116.8 (11.1)	116.8 (11.2)	117.3 (11.3)	
Diastolic blood pressure, mmHg	73.4 (7.9)	73.1 (8.0)	73.8 (7.8)	73.5 (7.9)	73.4 (8.0)	73.4 (7.9)	
Fasting glucose levels, mg/dL	90.2 (12.3)	90.1 (12.4)	90.4 (12.2)	89.9 (11.9)	90.2 (12.3)	90.2 (12.4)	
Total cholesterol, mg/dL	197.0 (36.7)	196.5 (37.1)	197.7 (36.2)	197.8 (35.9)	197.8 (36.1)	197.4 (36.8)	
Family history of heart disease, stroke or hypertension, %	12.2%	10.8%	13.9%	15.9%	16.5%	10.9%	
Family history of cancer, %	14.2%	13.1%	15.3%	17.2%	16.6%	14.5%	
Family history of diabetes, %	6.3%	5.4%	7.2%	8.5%	9.2%	5.7%	
Smoking status, %							
Never	68.1%	71.9%	59.1%	65.2%	68.8%	71.7%	
Previously	8.4%	5.8%	12.0%	12.7%	12.5%	8.8%	
Currently	23.6%	22.2%	28.9%	22.1%	18.8%	19.5%	
Alcohol Consumption, %							
Never	58.4%	64.5%	47.6%	50.5%	52.2%	59.3%	
2-3 times/month	16.4%	13.8%	21.3%	19.7%	18.8%	14.1%	
1-2 times/week	15.8%	12.4%	22.0%	20.2%	18.1%	14.5%	
≥3 times/week	9.5%	9.3%	9.1%	9.5%	10.8%	12.1%	
Incident myocardial infarction, n (%)	3,047 (1.2)	1,741 (1.2)	723 (1.1)	276 (1.1)	88 (1.3)	219 (1.4)	
Incident stroke, n (%)	16,134 (6.3)	9,689 (6.5)	3,333 (5.3)	1,482 (6.0)	390 (5.8)	1,240 (8.2)	
Incident hypertension, n (%)	120,203 (46.6)	65,964 (44.5)	30,623 (48.7)	12,617 (50.8)	3,294 (49.3)	7,705 (50.9)	
Incident Type 2 diabetes, n (%)	50,459 (19.6)	27,128 (18.3)	10,666 (6.5)	5,421 (21.8)	1,399 (21.0)	3,285 (21.7)	
Incident stomach cancer, n (%)	4,788 (1.9)	2,672 (1.8)	13,226 (21.0)	489 (2.0)	139 (2.1)	328 (2.2)	
Incident colon cancer, n (%)	2,711 (1.1)	1,424 (1.0)	1,160 (1.8)	314 (1.3)	90 (1.3)	191 (1.3)	
Incident rectum cancer, n (%)	1,494 (0.6)	809 (0.6)	692 (1.1)	154 (0.6)	46 (0.6)	107 (0.7)	
Incident lung cancer, n (%)	3,601 (1.4)	2,138 (1.4)	796 (1.3)	307 (1.2)	85 (1.3)	275 (1.8)	
Incident liver cancer, n (%)	2,620 (1.0)	1,423 (1.0)	680 (1.1)	263 (1.1)	75 (1.1)	179 (1.2)	
Incident pancreas cancer, n (%)	864 (0.3)	483 (0.3)	205 (0.3)	92 (0.4)	24 (0.4)	60 (0.4)	
Incident head & neck cancer, n (%)	656 (0.3)	377 (0.3)	144 (0.2)	73 (0.3)	15 (0.2)	47 (0.3)	
Incident kidney cancer, n (%)	589 (0.2)	301 (0.2)	153 (0.2)	75 (0.3)	16 (0.2)	44 (0.3)	
Incident gallbladder cancer, n (%)	400 (0.2)	219 (0.1)	83 (0.1)	43 (0.2)	16 (0.2)	39 (0.3)	
Incident esophagus cancer, n (%)	352 (0.1)	214 (0.1)	75 (0.1)	29 (0.1)	6 (0.09)	28 (0.2)	
Median follow-up period, years (interguartile range)	13.0 (12.2, 13.3)	13.0 (12.2, 13.3)	13.0 (12.2, 13.3)	13.0 (12.2, 13.3)	12.7 (12.2, 13.3)	12.6 (12.2, 13.3	

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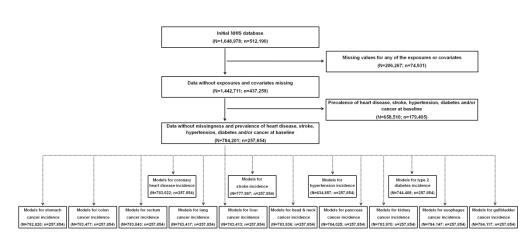
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A flow diagram. Note: "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data without missingness and prevalence of major diseases were used to create final analysis datasets for different incident disease outcomes; while the number of unique participants at baseline is the same for all incident disease outcomes, the total number of observations varied due to the nature of time-updated covariate analyses (i.e. censoring of subsequent time-updated covariates when an incident disease case occurs before the end date of repeated measures). Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million Korean adults (2002-2015) with the entire Korean population's health insurance system.

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Group		HR (95% CI)	Total cases(N	Unique) participants	s(n) Events(Cru n) rate
Myocardial infarction						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	1741	40.6
Exercise frequency: 1-2 times/week	→	0.87 (0.80, 0.95)	220601	62923	723	31.
Exercise frequency: 3-4 times/week	→	0.79 (0.70, 0.90)	92749	24836	276	29.
Exercise frequency: 5-6 times/week		0.98 (0.79, 1.22)	22457	6676	88	38.
Exercise frequency: Almost everyday		0.94 (0.82, 1.09)	45038	15135	219	46.
Stroke						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	9689	23
Exercise frequency: 1-2 times/week	→	0.86 (0.82, 0.89)	220601	62923	3333	14
Exercise frequency: 3-4 times/week	→	0.83 (0.79, 0.88)	92749	24836	1482	16
Exercise frequency: 5-6 times/week -	→	0.80 (0.73, 0.89)	22457	6676	390	17
Exercise frequency: Almost everyday		0.95 (0.90, 1.01)	45038	15135	1240	27
Hypertension						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	65964	23
Exercise frequency: 1-2 times/week	•	0.92 (0.90, 0.93)	220601	62923	30623	21
Exercise frequency: 3-4 times/week	+	0.86 (0.85, 0.88)	92749	24836	12617	20
Exercise frequency: 5-6 times/week	+	0.87 (0.84, 0.90)	22457	6676	3294	21
Exercise frequency: Almost everyday	+	0.95 (0.93, 0.97)	45038	15135	7705	26
Type 2 diabetes						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	27128	14
Exercise frequency: 1-2 times/week	+	0.92 (0.90, 0.94)	220601	62923	13226	16
Exercise frequency: 3-4 times/week	+	0.87 (0.84, 0.89)	92749	24836	5421	17
Exercise frequency: 5-6 times/week	→	0.88 (0.84, 0.93)	22457	6676	1399	16
Exercise frequency: Almost everyday	-	0.97 (0.93, 1.00)	45038	15135	3285	17
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Associations of exercise frequency with various incident cardiovascular disease outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of heart disease, stroke or hypertension (in models for myocardial infarction, stroke and hypertension) or diabetes (in models for Type 2 diabetes), smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million Korean adults (2002-2015) with the entire Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals BMJ Open: first published as 10.1136/bmjopen-2018-025590 on 13 March 2019. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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Group	HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	C ra
Stomach cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	2672	1
Exercise frequency: 1-2 times/week	0.90 (0.84, 0.97)	220601 92749	62923	1160 489	1
Exercise frequency: 3-4 times/week	0.87 (0.79, 0.96) 0.93 (0.78, 1.10)	92749 22457	24836 6676	489 139	1
Exercise frequency: 5-6 times/week	0.88 (0.78, 0.98)	45038	15135	328	1
	,				
Colon cancer Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	1424	7
Exercise frequency: 1-2 times/week	1.05 (0.95, 1.15)	220601	62923	692	8
Exercise frequency: 3-4 times/week	1.06 (0.93, 1.20)	92749	24836	314	1
Exercise frequency: 5-6 times/week	→ 1.14 (0.92, 1.41)	22457	6676	90	1
Exercise frequency: Almost everyday	0.97 (0.83, 1.12)	45038	15135	191	1
Rectum cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	809	4
Exercise frequency: 1-2 times/week	0.96 (0.85, 1.09)	220601	62923	378	4
Exercise frequency: 3-4 times/week	0.88 (0.74, 1.05)	92749	24836	154	4
Exercise frequency: 5-6 times/week	→ 1.00 (0.74, 1.35)	22457	6676	46	5 5
Exercise frequency: Almost everyday	0.95 (0.78, 1.16)	45038	15135	107	5
Lung cancer Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	2138	1
Exercise frequency: 1-2 times/week	0.90 (0.83, 0.98)	220601	62923	796	i
Exercise frequency: 3-4 times/week	0.80 (0.71, 0.91)	92749	24836	307	9
Exercise frequency: 5-6 times/week	0.81 (0.65, 1.01)	22457	6676	85	1
Exercise frequency: Almost everyday	0.93 (0.82, 1.05)	45038	15135	275	1
Liver cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	1423	7
Exercise frequency: 1-2 times/week	0.95 (0.87, 1.05)	220601	62923	680	8
Exercise frequency: 3-4 times/week	0.85 (0.75, 0.98)	92749	24836	263	8
Exercise frequency: 5-6 times/week	0.94 (0.74, 1.18)	22457	6676	75	9
Exercise frequency: Almost everyday	0.93 (0.79, 1.08)	45038	15135	179	9
Pancreas cancer	1 00 /1 00 1 57	100055		100	
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	483	2
Exercise frequency: 1-2 times/week	1.02 (0.86, 1.20)	220601	62923	205	2
Exercise frequency: 3-4 times/week	1.01 (0.81, 1.27)	92749 22457	24836 6676	92 24	2
Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	 0.97 (0.64, 1.46) 0.92 (0.70, 1.20) 	45038	15135	60	3
	0.32 (0.70, 1.20)	43030	15155	00	5
Head&Neck cancer Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	377	2
Exercise frequency: 1-2 times/week	0.76 (0.63, 0.93)	220601	62923	144	1
Exercise frequency: 3-4 times/week	0.92 (0.71, 1.19)	92749	24836	73	2
Exercise frequency: 5-6 times/week	0.73 (0.43, 1.22)	22457	6676	15	1
Exercise frequency: Almost everyday	0.92 (0.68, 1.25)	45038	15135	47	2
Kidney cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	301	1
Exercise frequency: 1-2 times/week	0.95 (0.78, 1.17)	220601	62923	153	1
Exercise frequency: 3-4 times/week	→ 1.10 (0.85, 1.42)	92749	24836	75	2
Exercise frequency: 5-6 times/week	→ 0.93 (0.56, 1.54) → 1.11 (0.81, 1.52)	22457 45038	6676 15135	16 44	1
	,				
Gallbladder cancer Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	219	1
Exercise frequency: 1-2 times/week	 0.98 (0.75, 1.27) 	220601	62923	83	1
Exercise frequency: 3-4 times/week	1.09 (0.78, 1.52)	92749	24836	43	1
Exercise frequency: 5-6 times/week	1.47 (0.88, 2.45)	22457	6676	16	1
Exercise frequency: Almost everyday	→ 1.30 (0.93, 1.84)	45038	15135	39	2
Esophagus cancer		100		~	
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	214	1
Exercise frequency: 1-2 times/week	0.86 (0.65, 1.12)	220601	62923	75	9
Exercise frequency: 3-4 times/week	0.78 (0.52, 1.15)	92749	24836	29 6	9
Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	 0.57 (0.25, 1.29) 0.90 (0.60, 1.33) 	22457 45038	6676 15135	6 28	7
Exercise requercy. Airrost everyday	+ 0.80 (0.00, 1.33)	40000	13135	20	

Associations of exercise frequency with various incident cancer outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of cancer, smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million Korean adults (2002-2015) with the entire Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

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Group		HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Cr) rat
Hypertension: Non-obese (BMI<25) Exercise Frequency: North (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	**	1.00 (1.00, 1.00) 0.92 (0.91, 0.94) 0.85 (0.83, 0.87) 0.86 (0.82, 0.90) 0.95 (0.92, 0.98)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	23 21 21 21
Hypertension: Obese (BMI≥25) Exercise frequency: None (Raference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Atimost everyday	<i>*</i> _	1.00 (1.00, 1.00) 0.93 (0.90, 0.95) 0.91 (0.88 0.94) 0.92 (0.87, 0.98) 0.98 (0.94, 1.02)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	23 20 20 20
Hypertension: Smoking - Never Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Alimost everyday	***	$\begin{array}{c} 1.00 & (1.00, 1.00) \\ 0.89 & (0.86, 0.91) \\ 0.82 & (0.81, 0.84) \\ 0.86 & (0.82, 0.89) \\ 0.93 & (0.90, 0.95) \end{array}$	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	22222
Hypertension: Smoking - Previously Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	≠	1.00 (1.00, 1.00) 0.91 (0.87, 0.95) 0.88 (0.83, 0.93) 0.87 (0.79, 0.96) 0.96 (0.88, 1.04)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	231222
Hypertension: Smoking - Currently Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.98 (0.95, 1.01) 0.97 (0.93, 1.01) 0.95 (0.88, 1.03) 1.03 (0.97, 1.09)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	22222
Hypertension: Alcohol consumption - Never Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	+	$\begin{array}{c} 1.00 & (1.00, 1.00) \\ 0.90 & (0.88, 0.92) \\ 0.84 & (0.81, 0.86) \\ 0.84 & (0.80, 0.88) \\ 0.93 & (0.90, 0.96) \end{array}$	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2222
Hypertension: Alcohol consumption - 2-3 times/month Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	++	1.00 (1.00, 1.00) 0.92 (0.89, 0.96) 0.84 (0.80, 0.88) 0.91 (0.84, 0.99) 1.01 (0.95, 1.08)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	221222
Hypertension: Alcohol consumption - 1-2 times/week Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	₹	1.00 (1.00, 1.00) 0.91 (0.88, 0.94) 0.91 (0.87, 0.95) 0.91 (0.84, 0.99) 0.96 (0.91, 1.03)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	231222
Hypertension: Alcohol consumption - 23 times/week Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	_	1.00 (1.00, 1.00) 0.98 (0.94, 1.02) 0.92 (0.87, 0.97) 0.93 (0.85, 1.03) 0.99 (0.92, 1.05)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2222
Hypertension: Men Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.94 (0.93, 0.96) 0.92 (0.90, 0.94) 0.93 (0.88, 0.97) 1.00 (0.97, 1.03)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	221222
Hypertension: Women Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	* + *	1.00 (1.00, 1.00) 0.87 (0.85, 0.89) 0.79 (0.76, 0.81) 0.82 (0.76, 0.87) 0.91 (0.88, 0.95)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	221221
Type 2 diabetes: Men Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	*	$\begin{array}{c} 1.00 & (1.00, \ 1.00) \\ 0.91 & (0.89, \ 0.94) \\ 0.87 & (0.84, \ 0.90) \\ 0.88 & (0.82, \ 0.94) \\ 0.93 & (0.88, \ 0.98) \end{array}$	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	27128 13226 5421 1399 3285	14 17 17 17
Type 2 diabetes; Women Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Alimost everyday	++ +-	1.00 (1.00, 1.00) 0.91 (0.88, 0.95) 0.86 (0.82, 0.90) 0.90 (0.83, 0.98) 1.03 (0.97, 1.08)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	27128 13226 5421 1399 3285	14 17 17 17
		1				

Results from assessment of effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequency and each incident disease outcome. Only associations for which the multiplicative interaction terms were statistically significant are presented. Cox regression models with age as the underlying timescale were adjusted for sex [not in models for effect modification by sex], body mass index [not in models for effect modification by body mass index], systolic blood pressure, fasting glucose levels, total cholesterol levels, family history [not in models for effect modification by family history of respective disease] of heart disease/stroke/hypertension (in models for myocardial infarction, stroke and hypertension), diabetes (in models for Type 2 diabetes) or cancer (in models for each cancer), smoking status [not in models for effect modification by smoking status] and alcohol consumption [not in models for effect modification by alcohol consumption]. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. P-values for multiplicative interactions with exercise frequency are as follows; Outcome hypertension: body mass index (0.049), smoking (<0.001), alcohol consumption (<0.001), family history of cardiovascular disease (0.029) and sex (<0.001); Outcome - lung cancer: body mass index (0.016), and; Outcome - type 2 diabetes: sex (0.012) - - - - Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million Korean adults (2002-2015) with

the entire Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

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Mycardial infarction ICD 10 codes I21-I23 Stroke ICD 10 codes I10, I11 and I15, systolic blood pressure 200 mmHg, or physiciar Type 2 diabetes ICD 10 codes C16 Colon cancer ICD 10 codes C20 Lung cancer ICD 10 codes C20 Lung cancer ICD 10 codes C20 Lung cancer ICD 10 codes C20 Head & neck cancer ICD 10 codes C20 Head & neck cancer ICD 10 codes C21 Head & neck cancer ICD 10 codes C24 Galibladder cancer ICD 10 codes C34 Liver cancer ICD 10 codes C34 Esophagus cancer ICD 10 codes C34 Galibladder cancer ICD 10 codes C34 Galibladder cancer ICD 10 codes C34 Storke cancer ICD 10 codes C34 Storke cancer ICD 10 codes C34 Galibladder cancer ICD 10 codes C35 Abbreviations: ICD – International Classification of Disease	Incident disease outcome	Definition
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Abbreviations: ICD – International Classification of Disease		

Supplementary Table 2. Participants' characteristics at 1^{st} , 2^{nd} , 3^{rd} , 4^{th} , 5^{th} and 6^{th} repeat-visit

Repeat visit	Variables	All (n=215,295)	Exercise frequency				
1 st			None (n=112,156)	1-2 times/week (n=57,777)	3-4 times/week (n=25,390)	5-6 times/week (n= 6,443)	Almost everyday (n=13,529)
	Sex, %						
	Men	51.1%	45.0%	61.8%	55.3%	50.6%	48.8%
	Women	48.9%	55.0%	38.2%	44.7%	49.4%	51.2%
	Age, years	52.7 (8.6)	53.6 (9.2)	50.9 (7.4)	51.3 (7.5)	52.3 (8.0)	55.6 (9.1)
	Body Mass Index, kg²/m 🛛 🦯 🚬 👝	23.5 (2.8)	23.4 (2.9)	23.6 (2.7)	23.7 (2.6)	23.6 (2.6)	23.7 (2.7)
	Systolic blood pressure, mmHg	120.5 (14.4)	120.6 (14.7)	120.4 (13.9)	120.0 (13.9)	119.6 (13.9)	121.4 (14.0
	Diastolic blood pressure, mmHg	75.7 (9.9)	75.6 (9.9)	75.9 (9.8)	75.5 (9.8)	75.2 (9.8)	75.7 (9.8)
	Fasting glucose levels, mg/dL	92.6 (18.5)	92.6 (18.8)	92.7 (17.4)	92.4 (17.8)	92.8 (21.0)	93.3 (20.2
	Total cholesterol, mg/dL	197.3 (36.2)	197.0 (36.8)	197.3 (35.6)	197.9 (35.1)	197.4 (35.9)	197.8 (36.
	Family history of heart disease, stroke or hypertension, %	12.6%	10.7%	14.2%	16.7%	16.7%	12.0%
	Family history of cancer, %	14.3%	12.7%	15.5%	17.4%	19.2%	14.5%
	Family history of diabetes, %	6.0%	5.0%	6.7%	8.2%	9.0%	5.8%
	Smoking status, %						
	Never	70.7%	74.8%	62.4%	68.9%	71.7%	74.8%
	Previously	8.6%	5.8%	11.9%	12.4%	11.9%	8.8%
	Currently	20.8%	19.4%	25.7%	18.7%	16.3%	16.4%
	Alcohol Consumption, %						
	Never	59.8%	66.9%	49.2%	52.7%	54.9%	61.8%
	2-3 times/month	15.6%	12.7%	20.5%	18.6%	18.2%	12.8%
	1-2 times/week	15.8%	11.8%	21.7%	19.9%	17.0%	14.8%
	≥3 times/week	8.8%	8.7%	8.6%	8.7%	10.0%	10.6%

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Supplementary Table 2	. Participants	' characteristics at 1 ^s	st , 2 nd , 3 rd , 4 th ,	, 5 th and 6 th	repeat-visit (cont.)
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Repeat visit	Variables	All (n=150,845)	Exercise frequency				
2 nd			None (n=73,660)	1-2 times/week (n=44,211)	3-4 times/week (n=19,593)	5-6 times/week (n=4,771)	Almost everyday (n= 8,610)
	Sex, %						
	Men	54.2%	47.0%	64.6%	57.9%	53.8%	53.5%
	Women	45.8%	53.0%	35.4%	42.1%	46.2%	46.5%
	Age, years	53.3 (8.3)	54.2 (8.9)	51.7 (7.2)	52.3 (7.4)	53.4 (7.8)	56.5 (9.1)
	Body Mass Index, kg²/m 🛛 🖊 🚬	23.5 (2.7)	23.4 (2.8)	23.6 (2.6)	23.7 (2.6)	23.6 (2.6)	23.6 (2.7)
	Systolic blood pressure, mmHg	120.9 (14.1)	121.0 (14.5)	120.7 (13.7)	120.4 (13.6)	120.3 (13.7)	122.0 (14.
	Diastolic blood pressure, mmHg	75.8 (9.6)	75.8 (9.7)	76.0 (9.5)	75.5 (9.4)	75.4 (9.4)	76.0 (9.8)
	Fasting glucose levels, mg/dL	93.2 (16.9)	93.1 (17.4)	93.5 (17.0)	93.1 (15.5)	93.5 (15.9)	93.7 (16.2
	Total cholesterol, mg/dL	197.6 (35.9)	197.7 (36.5)	197.4 (35.4)	197.8 (35.2)	196.7 (34.9)	198.1 (36.
	Family history of heart disease, stroke or hypertension, %	13.4%	11.2%	14.6%	17.5%	18.3%	13.1%
	Family history of cancer, %	14.9%	12.9%	16.4%	17.4%	19.7%	15.4%
	Family history of diabetes, %	6.3%	5.2%	7.1%	8.2%	9.0%	6.1%
	Smoking status, %						
	Never	71.0%	76.5%	62.3%	68.7%	71.2%	74.2%
	Previously	9.0%	5.5%	12.5%	13.1%	13.1%	9.4%
	Currently	20.0%	18.0%	25.3%	18.2%	15.8%	16.5%
	Alcohol Consumption, %						
	Never	59.0%	67.6%	48.1%	51.9%	54.1%	60.0%
	2-3 times/month	16.1%	12.6%	20.9%	19.0%	18.9%	13.6%
	1-2 times/week	16.7%	12.1%	22.8%	20.7%	17.5%	15.8%
	≥3 times/week	8.1%	7.8%	8.2%	8.3%	9.5%	10.7%

Supplementary Table 2. Participants' characteristics at 1st, 2nd, 3rd, 4th, 5th and 6th repeat-visit (cont.)

Repeat visit	Variables	All (n=80,639)	Exercise frequency				
3 rd			None (n= 36,123)	1-2 times/week (n=26,505)	3-4 times/week (n=11,432)	5-6 times/week (n=2,391)	Almost everyday (n=4,188)
	Sex, %						
	Men	63.1%	53.9%	73.0%	68.6%	64.5%	63.4%
	Women	36.9%	46.1%	27.0%	31.4%	35.6%	36.7%
	Age, years	52.3 (7.2)	52.9 (7.8)	51.2 (6.2)	51.9 (6.6)	52.8 (7.0)	55.2 (8.4)
	Body Mass Index, kg²/m 🛛 🖊 🚬 👝	23.5 (2.7)	23.3 (2.8)	23.6 (2.6)	23.7 (2.5)	23.7 (2.6)	23.7 (2.7)
	Systolic blood pressure, mmHg	121.1 (13.6)	120.9 (13.9)	120.9 (13.4)	121.0 (13.2)	120.6 (13.3)	122.0 (14.0
	Diastolic blood pressure, mmHg	76.1 (9.4)	76.0 (9.5)	76.4 (9.4)	76.1 (9.1)	75.6 (9.5)	76.3 (9.6)
	Fasting glucose levels, mg/dL	93.7 (16.8)	93.3 (17.1)	94.1 (16.7)	93.9 (15.9)	94.1 (16.5)	94.5 (17.0)
	Total cholesterol, mg/dL	197.1 (35.2)	197.1 (35.5)	197.4 (34.8)	196.9 (34.7)	196.5 (35.2)	196.7 (35.4
	Family history of heart disease, stroke or hypertension, %	13.5%	11.4%	14.8%	16.7%	18.6%	11.7%
	Family history of cancer, %	14.8%	13.0%	15.8%	17.8%	18.9%	14.7%
	Family history of diabetes, %	6.4%	5.3%	7.0%	8.0%	9.5%	6.2%
	Smoking status, %						
	Never	66.6%	73.8%	57.6%	63.9%	65.5%	68.8%
	Previously	10.7%	6.1%	14.0%	15.5%	16.6%	12.4%
	Currently	22.8%	20.2%	28.4%	20.6%	17.9%	18.7%
	Alcohol Consumption, %						
	Never	53.6%	64.2%	42.5%	47.2%	47.4%	53.9%
	2-3 times/month	18.5%	14.0%	23.7%	20.8%	21.4%	15.8%
	1-2 times/week	19.5%	14.0%	25.6 %	22.8%	20.7%	18.8%
	≥3 times/week	8.4%	7.8%	8.3%	9.2%	10.5%	11.5%

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Supplementary Table 2. Participants' characteristics at 1 st , 2 nd , 3 ^r	rd , 4 th , 5 th	and 6 th repeat-visit (cont.)
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Repeat visit	Variables	All (n=40,910)	Exercise frequency				
4 th			None (n=17,678)	1-2 times/week (n=14,624)	3-4 times/week (n= 5,685)	5-6 times/week (n=1,094)	Almost everyday (n=1,829)
	Sex, %						
	Men	72.3%	61.6%	81.1%	81.5%	78.2%	73.9%
	Women	27.7%	38.4%	18.9%	18.5%	21.9%	26.1%
	Age, years	50.9 (5.4)	51.2 (5.5)	50.6 (5.1)	50.7 (5.3)	51.0 (5.6)	52.6 (6.3)
	Body Mass Index, kg²/m 🛛 🦯 🚬 👝	23.5 (2.7)	23.3 (2.7)	23.7 (2.6)	23.8 (2.6)	23.8 (2.5)	23.7 (2.6)
	Systolic blood pressure, mmHg	121.4 (13.3)	120.9 (13.5)	121.7 (13.0)	121.5 (12.8)	121.5 (13.1)	122.7 (13.6
	Diastolic blood pressure, mmHg	76.6 (9.2)	76.2 (9.3)	77.0 (9.2)	76.8 (8.9)	76.8 (9.4)	77.2 (9.5)
	Fasting glucose levels, mg/dL 🛛 🖉 💊	93.9 (17.8)	93.3 (17.9)	94.4 (17.9)	94.3 (17.1)	94.0 (16.0)	94.9 (18.8)
	Total cholesterol, mg/dL	196.8 (35.0)	197.2 (35.5)	196.7 (34.6)	196.6 (34.2)	195.0 (34.3)	196.5 (34.9
	Family history of heart disease, stroke or hypertension, %	12.3%	10.4%	13.7%	14.2%	16.3%	11.6%
	Family history of cancer, %	13.8%	12.6%	14.7%	15.0%	16.3%	13.5%
	Family history of diabetes, %	5.7%	4.8%	6.2%	6.9%	7.5%	6.7%
	Smoking status, %						
	Never	60.6%	69.5%	51.9%	55.5%	57.3%	62.0%
	Previously	12.2%	6.9%	15.1%	18.7%	18.7%	15.7%
	Currently	27.2%	23.7%	33.0%	25.8%	24.0%	22.4%
	Alcohol Consumption, %						
	Never	48.1%	60.0%	38.0%	39.1%	39.9%	45.4%
	2-3 times/month	20.5%	15.5% 🧹 🦳	24.9%	24.3%	24.0%	19.7%
	1-2 times/week	22.4%	16.2%	28.4%	26.3%	22.6%	22.9%
	≥3 times/week	9.0%	8.2%	8.7%	10.3%	13.6%	12.0%

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Supplementary Table 2. Participants' characteristics at 1st, 2nd, 3rd, 4th, 5th and 6th repeat-visit (cont.)

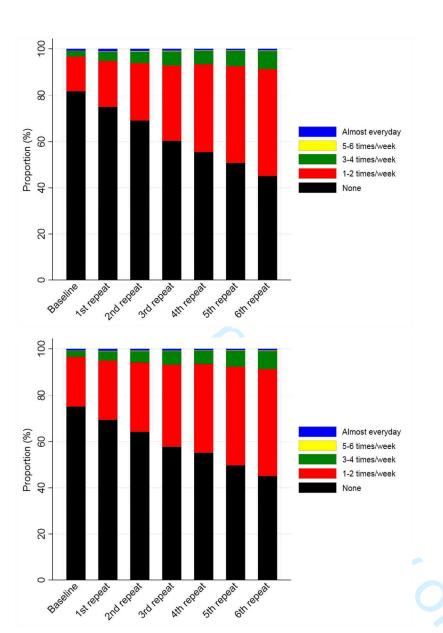
Repeat visit	Variables	All (n= 26,356)	Exercise frequency				
5 th			None (n=10,771)	1-2 times/week (n=9,807)	3-4 times/week (n=3,884)	5-6 times/week (n=724)	Almost everyday (n=1,170)
	Sex, %						
	Men	73.7%	62.6%	81.6%	82.4%	81.2%	76.9%
	Women	26.3%	37.4%	18.4%	17.6%	18.8%	23.0%
	Age, years	51.1 (4.9)	51.4 (5.1)	50.8 (4.7)	51.0 (4.7)	51.4 (5.0)	52.1 (5.6)
	Body Mass Index, kg²/m 🛛 🦯 🚬 👝	23.5 (2.6)	23.3 (2.7)	23.7 (2.6)	23.8 (2.4)	23.7 (2.5)	23.8 (2.6)
	Systolic blood pressure, mmHg	121.4 (13.0)	121.0 (13.4)	121.8 (12.9)	121.6 (12.6)	120.8 (12.9)	121.5 (12.
	Diastolic blood pressure, mmHg	76.6 (9.1)	76.2 (9.1)	77.1 (9.0)	76.8 (8.8)	76.7 (8.6)	76.4 (9.0)
	Fasting glucose levels, mg/dL	94.3 (17.6)	93.7 (18.1)	94.6 (17.3)	94.7 (16.6)	94.6 (15.9)	95.4 (18.7
	Total cholesterol, mg/dL	197.1 (34.5)	197.7 (34.8)	196.7 (34.2)	196.4 (33.8)	195.2 (34.2)	198.2 (37.
	Family history of heart disease, stroke or hypertension, %	12.6%	11.3%	13.4%	14.3%	13.8%	10.9%
	Family history of cancer, %	14.3%	13.2%	15.1%	14.9%	17.8%	13.5%
	Family history of diabetes, %	5.9%	4.9%	6.4%	6.7%	7.2%	8.6%
	Smoking status, %						
	Never	58.9%	68.1%	50.8%	54.4%	57.0%	58.5%
	Previously	13.1%	7.1%	16.0%	19.3%	19.8%	19.7%
	Currently	28.0%	24.8%	33.2%	26.2%	23.2%	21.9%
	Alcohol Consumption, %						
	Never	46.3%	57.9%	37.6%	38.3%	41.3%	42.9%
	2-3 times/month	21.7%	16.7%	25.8%	24.7%	22.2%	22.3%
	1-2 times/week	23.4%	17.4%	28.0%	27.3%	26.0%	25.0%
	≥3 times/week	8.6%	8.1%	8.5%	9.8%	10.5%	9.7%

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Supplementary Table 2	. Participants'	' characteristics at 1 ^s	st , 2 nd , 3	rd , 4 th , 5	^{5th and 6th repeat-visit (cont.)}	
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Repeat visit	Variables	All (n= 12,302)	Exercise frequency				
6 th			None (n= 4,684)	1-2 times/week (n=4,754)	3-4 times/week (n=1,929)	5-6 times/week (n=358)	Almost everyday (n=577)
	Sex, %						
	Men	76.2%	64.2%	83.8%	84.7%	80.7%	80.4%
	Women	23.8%	35.8%	16.2%	15.3%	19.3%	19.6%
	Age, years	51.3 (4.5)	51.6 (4.7)	51.0 (4.2)	51.0 (4.4)	51.2 (4.3)	52.0 (5.1)
	Body Mass Index, kg²/m 🛛 🖊 📉	23.6 (2.6)	23.3 (2.7)	23.7 (2.6)	23.8 (2.4)	23.6 (2.2)	23.7 (2.5)
	Systolic blood pressure, mmHg	121.5 (12.8)	121.2 (13.0)	121.6 (12.6)	121.7 (12.6)	121.0 (12.5)	122.1 (12.
	Diastolic blood pressure, mmHg	76.7 (9.0)	76.4 (9.0)	77.0 (8.9)	77.0 (9.0)	76.0 (8.7)	76.3 (9.0)
	Fasting glucose levels, mg/dL	94.6 (18.5)	93.7 (18.8)	95.1 (18.7)	94.9 (16.6)	95.1 (18.4)	95.7 (20.1
	Total cholesterol, mg/dL	197.1 (34.5)	197.9 (35.0)	197.1 (34.2)	195.8 (34.3)	192.0 (32.2)	197.4 (34.
	Family history of heart disease, stroke or hypertension, %	13.2%	11.7%	13.7%	15.5%	14.3%	12.7%
	Family history of cancer, %	14.5%	12.9%	15.5%	15.7%	15.1%	14.9%
	Family history of diabetes, %	6.4%	5.5%	6.4%	7.3%	7.3%	9.5%
	Smoking status, %						
	Never	56.9%	66.6%	48.7%	53.6%	57.3%	57.4%
	Previously	14.0%	7.0%	17.3%	20.4%	16.8%	21.1%
	Currently	29.1%	26.5%	34.1%	26.0%	26.0%	21.5%
	Alcohol Consumption, %						
	Never	43.7%	56.5%	35.0%	36.4%	40.5%	37.8%
	2-3 times/month	22.8%	17.0%	27.2%	24.9%	24.6%	24.8%
	1-2 times/week	24.8%	17.6%	30.0%	28.3%	26.5%	27.4%
	≥3 times/week	8.8%	8.8%	7.9%	10.4%	8.4%	10.1%



Supplementary Figure 1. Changes in proportions of exercise frequency categories across 7 time points in all 257,854 individuals who provided data at each respective assessment visit (top panel), and 12,302 individuals who provided data from all 7 assessment visits (bottom panel).

Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 403356 148284 1741 40.6 Exercise frequency: 3-4 times/week 0.98 (0.90, 1.07) 220601 62923 723 31.7 Exercise frequency: 3-4 times/week 0.98 (0.79, 1.22) 22457 6676 88 38.2 Exercise frequency: Almost everyday 0.97 (0.84, 1.12) 45038 15135 219 46.4 Stroke 1.00 (1.00, 1.00) 403356 148284 9689 232. Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 403356 148284 9689 232. Exercise frequency: 3-4 times/week + 0.83 (0.79, 0.88) 92749 24836 1482 160. Exercise frequency: 4.1-2 times/week + 0.83 (0.79, 0.88) 92749 24836 1482 160. Exercise frequency: 3-4 times/week + 0.83 (0.79, 0.88) 92749 24836 1482 160. Exercise frequency: Almost everyday + 0.83 (0.79, 0.88) 92749 24836 1482 160. Intervise frequency: Almost everyday + 0.95 (0.90, 1.01) 45038 15135 1240 272. Hypertension Exercise frequency: 1-2 times/week	Group		HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Crude rate
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Exercise frequency: 1-2 times/week 1.00 (0.98, 1.02) 220601 62923 13226 167 Exercise frequency: 3-4 times/week 0.91 (0.89, 0.94) 92749 24836 5421 1743 0.92 (0.88, 0.97) 22457 6676 1399 168 1.01 (0.97, 1.04) 45038 15135 3285 1733 	Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	27128	1457
Exercise frequency: 3-4 times/week 0.91 (0.89, 0.94) 92749 24836 5421 1744 0.92 (0.88, 0.97) 22457 6676 1399 168 0.92 (0.88, 0.97) 22457 6676 1399 168 1.01 (0.97, 1.04) 45038 15135 3285 1733 1.01	Contraction of the second state of the second	+					
Exercise frequency: 5-6 times/week 0.92 (0.88, 0.97) 22457 6676 1399 168 1.01 (0.97, 1.04) 45038 15135 3285 1733 Image: Contract of the symplectic con		+					
Exercise frequency: Almost everyday 1.01 (0.97, 1.04) 45038 15135 3285 1733		<u> </u>					
		Ĩ	1.01 (0.01, 1.04)			5200	
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	.0	1	1.5				

BMJ Open: first published as 10.1136/bmjopen-2018-025590 on 13 March 2019. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Group		HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Crud rate
tomach cancer						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	2672	143.6
Exercise frequency: 1-2 times/week		1.01 (0.95, 1.09)	220601	62923	1160	146.6
Exercise frequency: 3-4 times/week	-+	0.94 (0.85, 1.03)	92749	24836	489	157.4
Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		0.99 (0.83, 1.17) 0.93 (0.83, 1.04)	22457 45038	6676 15135	139 328	167 173.5
	•	0.00 (0.00, 1.04)	40000	10100	020	110.0
Colon cancer Exercise frequency: None (Reference)	1	1.00 (1.00, 1.00)	403356	148284	1424	76.5
Exercise frequency: 1-2 times/week	↓	- 1.13 (1.03, 1.24)	220601	62923	692	87.4
Exercise frequency: 3-4 times/week	· · · · · · · · · · · · · · · · · · ·	1.12 (0.99, 1.27)	92749	24836	314	101.1
Exercise frequency: 5-6 times/week	+ ●	➡ 1.20 (0.97, 1.48)	22457	6676	90	108.2
Exercise frequency: Almost everyday		1.02 (0.87, 1.18)	45038	15135	191	101
Rectum cancer		4 00 (4 00 4 00)	100050	110001	000	40.5
Exercise frequency: None (Reference)	<u> </u>	1.00 (1.00, 1.00)	403356 220601	148284 62923	809 378	43.5
Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week		1.07 (0.94, 1.21) 0.95 (0.80, 1.13)	92749	24836	154	47.8
Exercise frequency: 5-6 times/week		→ 1.07 (0.79, 1.43)	22457	6676	46	55.3
Exercise frequency: Almost everyday		1.01 (0.82, 1.23)	45038	15135	107	56.6
ung cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	2138	114.9
Exercise frequency: 1-2 times/week	· -+-	0.97 (0.89, 1.05)	220601	62923	796	100.6
Exercise frequency: 3-4 times/week		0.81 (0.72, 0.91)	92749	24836	307	98.8
Exercise frequency: 5-6 times/week		0.80 (0.65, 1.00)	22457 45038	6676 15135	85 275	102.1 145.4
Exercise frequency: Almost everyday		0.94 (0.83, 1.07)	40000	10100	215	145.4
iver cancer Exercise frequency: None (Reference)	L L	1.00 (1.00, 1.00)	403356	148284	1423	76.5
Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week	T_	1.00 (1.00, 1.00) 1.07 (0.97, 1.17)	220601	62923	680	76.5 85.9
Exercise frequency: 3-4 times/week	T	0.91 (0.80, 1.04)	92749	24836	263	84.7
Exercise frequency: 5-6 times/week		 0.91 (0.80, 1.04) 0.99 (0.78, 1.24) 	22457	6676	75	90.1
Exercise frequency: Almost everyday	-	0.99 (0.84, 1.15)	45038	15135	179	94.7
ancreas cancer						
Exercise frequency: None (Reference)	•	1.00 (1.00, 1.00)	403356	148284	483	26
Exercise frequency: 1-2 times/week		 1.05 (0.89, 1.24) 1.03 (0.82, 1.20) 	220601	62923	205	25.9
Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week		1.03 (0.82, 1.29) 0.98 (0.65, 1.48)	92749 22457	24836 6676	92 24	29.6 28.8
Exercise frequency: Almost everyday		0.93 (0.71, 1.22)	45038	15135	60	31.7
lead&Neck cancer						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	377	20.3
Exercise frequency: 1-2 times/week		0.86 (0.71, 1.05)	220601	62923	144	18.2
Exercise frequency: 3-4 times/week		0.96 (0.75, 1.24)	92749	24836	73	23.5
Exercise frequency: 5-6 times/week	•	 0.75 (0.44, 1.25) 0.96 (0.71, 1.20) 	22457	6676	15	18
Exercise frequency: Almost everyday		0.96 (0.71, 1.29)	45038	15135	47	24.9
idney cancer Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	301	16.2
Exercise frequency: 1-2 times/week	_ _	→ 1.10 (0.90, 1.34)	220601	62923	153	19.3
Exercise frequency: 3-4 times/week	•	➡ 1.20 (0.93, 1.54)	92749	24836	75	24.1
Exercise frequency: 5-6 times/week		→ 0.98 (0.59, 1.62)	22457	6676	16	19.2
Exercise frequency: Almost everyday		→ 1.17 (0.85, 1.60)	45038	15135	44	23.3
allbladder cancer			1000000	4 4000 5	212	
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	219	11.8
Exercise frequency: 1-2 times/week		 0.97 (0.75, 1.25) 1.09 (0.79, 1.52) 	220601	62923	83	10.5
Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week		→ 1.09 (0.79, 1.52) → 1.48 (0.89, 2.45)	92749 22457	24836 6676	43 16	13.8 19.2
Exercise frequency: Almost everyday		 → 1.48 (0.89, 2.43) → 1.32 (0.94, 1.86) 	45038	15135	39	20.6
sophagus cancer						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	214	11.5
Exercise frequency: 1-2 times/week		0.91 (0.70, 1.19)	220601	62923	75	9.5
Exercise frequency: 3-4 times/week		0.76 (0.51, 1.12)	92749	24836	29	9.3
Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	• •	 0.56 (0.25, 1.26) 0.93 (0.62, 1.37) 	22457	6676 15135	6 28	7.2
Exercise inequency. Almost everyday		→ 0.93 (0.62, 1.37)	45038	19199	20	14.6
	I I .3 1	l 1.3				

Supplementary Figure 2. Associations of exercise with incident myocardial infarction, stroke, hypertension and Type 2 diabetes (top panel) and various incident cancer outcomes (bottom panel). Note: Cox regression models using age as the underlying timescale were not adjusted for any confounders. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

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Exercise and incidence of myocardial infarction, stroke, hypertension, type 2 diabetes and site-specific cancers: A prospective cohort study.

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Title: Exercise and incidence of myocardial infarction, stroke, hypertension, type 2 diabetes

and site-specific cancers: A prospective cohort study.

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Abstract

Objective: The objective of this study was to examine the longitudinal associations of exercise frequency with the incidence of myocardial infarction, stroke, hypertension, type 2 diabetes and 10 different cancer outcomes.

Design: A prospective cohort study.

Setting: Physical examination data linked with the entire South Korean population's health insurance system: from 2002 to 2015

Participants: 257,854 South Korean adults who provided up to 7 repeat-measures of exercise (defined as exercises causing sweat) and confounders.

Primary outcome measures: Each disease incidence was defined using both fatal and nonfatal health records (a median follow-up period of 13 years).

Results: Compared with no exercise category, the middle categories of exercise frequency (3-4 or 5-6 times/week) showed the lowest risk of myocardial infarction (hazard ratio[HR]: 0.79; 95% confidence interval[CI]: 0.70-0.90), stroke (HR: 0.80; 95%CI: 0.73-0.89), hypertension (HR: 0.86; 95%CI: 0.85-0.88), type 2 diabetes (HR: 0.87; 95%CI: 0.84-0.89), stomach (HR: 0.87; 95%CI: 0.79-0.96), lung (HR: 0.80; 95%CI: 0.71-0.91), liver (HR: 0.85; 95%CI: 0.75-0.98) and head & neck cancers (HR: 0.76; 95%CI: 0.63-0.93; for 1-2 times/week), exhibiting J-shaped associations. There was, in general, little evidence of effect modification by body mass index, smoking, alcohol consumption, family history of disease, and sex in these associations.

Conclusions: Moderate levels of sweat-inducing exercise showed the lowest risk of myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancers. Public health and lifestyle interventions should, therefore, promote moderate levels of sweat-causing exercise as a behavioural prevention strategy for non-communicable diseases in a wider population of East Asians.

1 2	
3	Keywords: exercise, non-communicable disease,
4 5	disease, hypertension, cancer
6 7	
8	
9 10	Article Sum
11 12	
13	Strengths and limitations of this study
14 15	 This study is the first to investigate the long
16 17	
18	various cardiovascular disease and cancer
19 20	dataset of South Korean adults (n=257,854
21 22	measures of exercise and all confounders
23	dilution.
24 25	• A limitation is that no strong inference can
26 27	disease relationships.
28 29	
30	 Findings of this study may not be generalized
31 32	origins.
33 34	Introduct
35 36	
37	Prevention and control of non-communicable dise
38 39	health priority. At present, 40 million deaths per ye
40 41	deaths globally, are attributable to non-communication
42	deaths due to non-communicable diseases, such
43 44	diabetes ⁵ and cancer, ⁶ has increased dramatically
45 46	
47 48	standardised cardiovascular disease and cancer r
49	levels ⁷ have declined. ^{8,9} However, trends in these
50 51	populations, particularly with less favourable chan
52 53	compared with Western populations. For example
54	increased more rapidly, while the age-standardise
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cohort, epidemiology, cardiovascular

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- gitudinal associations of exercise with r incidence using a large-scale cohort 4) who provided up to 7 repeated in order to minimise the risk of regression
- be drawn about the exercise-incident
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ion

ases is a contemporary global public ear, which accounts for nearly 70% of total able diseases.^{1,2} Moreover, the number of as cardiovascular disease,³ hypertension,⁴ over the past few decades, although ageates as well as systolic blood pressure disease traits have varied across different ges observed in East Asian populations , the prevalence of diabetes¹⁰ has d prevalence of cardiovascular disease³

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and systolic blood pressure levels⁷ have fallen less steeply in East Asians in comparison with Westerners.

In addition, adults in East Asia tend to have higher prevalence of physical inactivity,¹¹ which is one of the four target behaviours (including unhealthy diet, tobacco use and harmful use of alcohol) that have been set as the global focus to reduce the risk of non-communicable diseases.¹² The beneficial impacts of increased physical activity on various noncommunicable outcomes have been demonstrated by numerous previous investigations. However, the majority of previous research has been predicated on evidence from Western populations, thereby limiting its application to other populations including East Asians. As such, little is currently known about levels of physical activity including exercise in relation to non-communicable diseases in East Asian populations as compared with Western populations.¹³ Another critical gap in the existing literature is the use of data measured only at a single point in time (i.e., baseline), in which case physical activity or exercise levels are assumed to remain constant over time. This methodology, therefore, precludes the fact that individuals' physical activity or exercise levels change with time, and hence may increase the potential for regression dilution.¹⁴ Furthermore, it is well-known that temporal changes occur in other traditional behavioural and metabolic risk factors for non-communicable diseases, such as adiposity levels.^{15,16} smoking.¹⁷ glucose levels¹⁸ and total cholesterol levels.¹⁹ exhibiting different patterns of changes between East Asian and Western populations. Nevertheless, no previous research of East Asians or Westerners took into account changes in these risk markers in understanding the relationships between physical activity and noncommunicable diseases. Moreover, the dose-response relationship between physical activity and various non-communicable disease outcomes has remained unclear in East Asians. Therefore, the purpose of this research was to explore the dose-response relationships between exercise frequency and various types of incident non-communicable diseases, such as myocardial infarction, stroke, hypertension, type 2 diabetes and site-specific cancers,

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using a large-scale prospective cohort of South Korean adults with multiple repeated measures of exercise frequency and other risk markers.

Methods

Study design and participants

This study is based on data from the National Health Insurance Service - Health Screening (NHIS-HEALS) cohort dataset,²⁰ which is a nationally representative random sample (stratified by 2 groups of sex [males and females], 18 groups of age ranges [less than 1 year, 1-4 years, every 5 years between 5-79 years, and more than 80 years], 3 groups of employment status [insured employees, self-employed individuals and medical aid beneficiaries] and 41 groups of income levels [upper 20% for insured employees, lower 20% for insured self-employed individuals and the lowest level for medical aid beneficiaries]²¹) of over 500,000 South Korean adults aged 40-79 years between 2002 and 2003 made available by the NHIS. The NHIS is a single health insurance system in South Korea, which manages and maintains information on the entire South Korean population's healthcare utilization; it is mandatory for all South Koreans to take part in the national health insurance system. The NHIS is also responsible for maintaining national health examination programs involving data from general health examinations of all insured employees, self-employed individuals and medical aid beneficiaries aged over 40 years; it is recommended for them to perform the health examination at least every two years. The health examination involves collection of information on body composition, blood profiles, blood pressure, self-reported lifestyles, self-reported physician-diagnosed disease, and self-reported family history of disease.

The NHIS-HEALS cohort includes a wide variety of information collected between 2002 and 2015: health examination data and demographic and eligibility data (e.g., in-patient and outpatient hospital records, medical bill, health insurance and medical aid beneficiaries). In the present analysis, we utilised health examination data collected between 2002 and 2008 to define the exercise frequency and all confounders. There was a change in the type of self-

report methods in 2009; hence, health examination data collected in or after 2009 were not considered in the analysis due to the inability to harmonise variables. However, we used full follow-up data accrued from 2002 until 2015. This research was approved by the Institutional Review Board (4-2017-0051) of the Yonsei University's Severance Hospital in Republic of Korea.

Exposure

The primary exposure variable of this study was exercise frequency, assessed using questionnaires administered during the health examinations. The specific question asked was "How many times per week do you engage in exercise that causes sweating?" Participants were asked to choose only one of the following 5 possible answers: None, 1-2 times/week, 3-4 times/week, 5-6 times/week and almost every day.

Outcomes

In the present study, we evaluated 14 incident disease outcomes, namely, myocardial infarction; stroke, hypertension; type 2 diabetes mellitus; and stomach, colon, rectum, lung, liver, head & neck, pancreatic, kidney, gall bladder and esophagus cancers. Participants' inpatient and out-patient hospital records (i.e., non-fatal status) and death records (i.e., fatal status) obtained through linkage with Statistics Korea were both classified according to the International Classification of Disease (ICD)-10 codes to classify different incidence types (Supplementary Table 1). Additionally, blood pressure (e.g., systolic \geq 140 mm Hg, diastolic \geq 90 mm Hg) and fasting glucose levels (e.g., \geq 126 mg/dL), both of which were measured during physical examinations, were used in conjunction with physicians' diagnosis information and ICD-10 codes to define incident hypertension and type 2 diabetes, respectively. Each incident disease cases. Incident disease cases were adjudicated using hospital and death records collected through December 31st, 2015. The median follow-up was 13.0 years (interquartile range: 10.2-11.3 years)

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Other covariates

The following covariates were included as confounders in the analyses: sex, body mass index (weight in kilograms (kg) divided by height in meters squared (m^2)), systolic blood pressure, fasting glucose, total cholesterol, family history of heart disease, stroke or hypertension [only in models for incident myocardial infarction, stroke or hypertension], family history of diabetes [only in models for type 2 diabetes], family history of cancer [only in models for incident cancer outcomes], smoking status (never, previously, currently) and alcohol consumption (never, 2-3 times/month, 1-2 times/week, \geq 3 times/week).

Statistical analysis

Analyses were performed to summarise descriptive statistics (e.g., means, standard deviations, frequency, and proportions) of each covariate and incident disease outcome for all participants and by exercise frequency category. Cox regression with age as the underlying time scale was used to estimate the associations of exercise frequency with each incident disease outcome, with adjustment for all the above-mentioned confounders as well as without any adjustment. Hazard ratios along with corresponding 95% confidence intervals were calculated to evaluate relative risk of each incident disease outcome. Data were structured to enable the inclusion of exercise frequency and all confounders from both baseline and up to 6 repeated measures as time-updated covariates. This approach takes into account changes in exercise frequency as well as each confounder over time in relation to disease incidence. Individuals who reported no exercise served as a reference group for all comparisons. Effect modification by body mass index (<25, ≥ 25 kg²/m), smoking status, alcohol consumption, family history of disease and sex was also examined based on Wald tests of interaction terms in the fully adjusted models for each incident disease outcome. Visual inspections of log-log plots provided support for the assumptions of proportional hazards for all covariates. A sensitivity analysis where incident disease cases occurring during the first 2 years of follow-up were removed was performed to address reverse

causality. Analyses were performed in Stata/SE Version 14 (StataCorp LP, College Station, TX).

Patient and Public Involvement.

Neither patients nor members of the public were involved in this study.

Results

Of an initial sample of 512,190 individuals, 74,931 had missing data on at least one of the model covariates, and 179,405 had self-reported physician-diagnosed heart attack, stroke, hypertension (additionally, systolic \geq 140 mm Hg or diastolic \geq 90 mm Hg), diabetes (additionally, fasting glucose levels \geq 126 mg/dL) or cancer at baseline, respectively. Excluding these individuals resulted in a final sample for analysis of 257,854 individuals (Figure 1).

Individuals provided up to 7 measures of exercise frequency and each confounder (i.e., baseline plus 6 repeated measures). Participants' characteristics at baseline are summarised in Table 1. Supplementary Table 2 summarises participants' characteristics at each repeat assessment. Individuals in the categories of 1-2, 3-4 or 5-6 times/week of exercise were slightly younger, but showed higher proportions of family history of disease and lower proportions of never smoking or drinking alcohol, compared with those in the categories of none or almost every day of exercise. Across the seven time points (Supplementary Figure 1), the proportion of individuals who reported no exercise decreased while the proportion who reported 1-2 or 3-4 times/week of exercise increased; there were no noticeable changes for the categories of 5-6 times/week or almost every day of exercise. Overall, J-shaped associations were found between exercise frequency and incident myocardial infarction, stroke, hypertension and type 2 diabetes. Hazard ratios for these diseases were lowest in the middle categories of exercise frequency (e.g., 3-4 or 5-6 times/week) (Figure 2). There were no associations for the most frequent exercise category

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(e.g., almost every day) with the incidence of myocardial infarction, stroke and type 2 diabetes.

J-shaped associations were also found for incident stomach, lung, liver and head & neck cancers (Figure 3). Higher exercise frequencies (e.g., 1-2, 3-4 times/week and almost every day) were associated with lower hazards of incident stomach cancer. No statistical significance was observed for incident colon, rectum, pancreas, kidney, gallbladder and esophagus cancers. Crude event rates per 100,000 person-years in the middle categories of exercise frequency were relatively lower for incident rectum, and esophagus cancers, but higher for incident pancreas, kidney and gallbladder cancers. Cox regression models with no adjustment for confounders (Supplementary Figure 2) and a sensitivity analysis (Supplementary Figure 3) in which incident cases occurring in the first 2 years of follow-up were removed both revealed nearly identical patterns of associations as the main analyses. Figure 4 shows comparisons of results that showed statistical significance for multiplicative interaction terms between exercise frequency and each incident disease outcome. Strong Jshaped associations for incident hypertension were identified at each level of body mass index. J-shaped associations of exercise frequency with incident hypertension were strong only in the more favourable levels of smoking (e.g., never, previously) and alcohol consumption (e.g., never, 2-3 times/month, 1-2 times/week); no or weak associations were identified in the most harmful level of smoking (e.g., current smokers) and alcohol consumption (e.g., \geq 3 times/week). J-shaped associations were evident at all levels of family history of CVD and sex for incident hypertension, and sex for incident type 2 diabetes. Exercise frequency was associated with incident lung cancer in non-obese individuals, but there was no evidence of association in obese individuals. All comparisons stratified by each potential effect modifier are presented in Supplementary Figures 4 and 5.

Discussion

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This is the first investigation examining the prospective associations of exercise with various incident non-communicable disease outcomes using multiple repeated measures of covariates in East Asian populations. We identified J-shaped associations of sweat-inducing exercise with incident myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancers, with the greatest benefits being observed in the middle categories of exercise frequency (e.g., 3-4 or 5-6 times/week): 1-2 times/week for head & neck cancer. These findings provide two important clinical and public health implications. First, prevention and management of non-communicable diseases in East Asians may benefit considerably from employing an exercise promotion approach in the context of combined non-communicable disease prevention. Mechanism research indicates that cardiovascular disease and type 2 diabetes have similar biological pathways relating to exercise.^{22,23} so an integrated prevention approach can be applied to control and manage these two diseases at a minimum.⁵ Moreover, regular participation in exercise can induce favourable changes in intermediate cardiometabolic risk markers.²⁴ which are important predictors of typical non-communicable diseases. Hence, promoting exercise has great potential to act as an integrative behavioural strategy for preventing and controlling various non-communicable diseases simultaneously in East Asian populations.

Second, individuals who engage in exercise 3-4 or 5-6 times/week, rather than every day, may be able to reduce their risk of developing myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung and liver cancers: 1-2 times/week for head & neck cancer. Similar J-shaped associations between high intensity exercise (e.g., running) and cardiovascular disease risk have also been reported in previous cohort studies of Western^{25,26} and Japanese adults.²⁷ Nevertheless, the present study as well as previous research²⁵⁻²⁷ found that the risk of developing cardiovascular events in individuals who had the highest level of exercise was not noticeably higher compared with those who had the lowest level of exercise. No previous research in East Asians has found such J-shaped relationships between exercise or physical activity and other incident disease outcomes such as hypertension,²⁸⁻³² diabetes³³⁻⁴⁰ and different type of cancers.⁴¹⁻⁴⁷ However, previous meta-

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analyses of cohort studies comprising predominantly Westerners found leisure-time physical activity to have curvilinear (but not J-shaped) associations with the incidence of type 2 diabetes,⁴⁸ and linear associations with the incidence of hypertension⁴⁹ and various site-specific cancers (liver, lung, head & neck, kidney, colon, rectal, bladder, gastric cardia, breast, endometrial, myeloid leukemia, myeloma, esophageal adenocarcinoma).⁵⁰ While additional research is needed to confirm the J-shaped associations of exercise with various incident diseases in other samples of East Asians, findings of this research provide a strong rationale for development and implementation of public health policies and clinical trials aimed at promoting a moderate level of sweat-causing exercise to minimise the risk of myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancers.

Another finding of this research is that associations of sweat-inducing exercise with hypertension were modified by body mass index, smoking, alcohol consumption, family history of cardiovascular disease and sex: lung cancer by body mass index and type 2 diabetes by sex. Notably, exercise frequency was not associated with hypertension in individuals who are smokers or drinking alcohol \geq 3 times/week (except for 3-4 times/week of exercise). This observation provides some evidence that the harmful impacts of smoking or binge drinking on hypertension⁵¹⁻⁵³ may not be offset completely by exercise. This, in turn, appears to advocate for the need for implementing a combined hypertension prevention strategy targeting promotion of exercise in conjunction with smoking cessation and reductions in alcohol consumption in East Asians.¹³ For lung cancer, the null associations in individuals with body mass index \geq 25 may be indicative of potential residual confounding through reported bias in smoking behaviours. Nonetheless, there was little evidence for effect modification for other disease comparisons, highlighting the importance of promoting exercise for the prevention of various non-communicable diseases in individuals at different levels of body mass index, smoking, alcohol consumption, family history of disease and sex.

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This study has several notable strengths. First, we used data from a large prospective cohort study in which exercise and other risk markers were assessed on multiple occasions (up to 7 times). Nearly 84% and 5% of the full participants provided 1 and 6 repeated measures of all covariates, respectively. Compelling evidence indicates that the risk of regression dilution can be reduced using repeated measures of exposure and confounders.¹⁴ Moreover, we examined the dose-response relationship of exercise frequency with a wide variety of specific types of incident non-communicable disease outcomes simultaneously using inpatient and out-patient diagnosis data as well as mortality data. The large sample size (n=257,854) is another strength.

This study has some limitations. Findings of this study may not be generalizable to adult populations of other ethnic origins. Due to the observational nature of this research, no strong inference can be drawn about the exercise-incident disease relationships. In addition, the accuracy of hospital admission records is uncertain, although the accuracy of death records from Statistics Korea was found to be 92% in previous research.⁵⁴ No information about medication use was available in the cohort data, so we could not use it as a potential confounder and another condition when defining disease status (e.g., hypertension, type 2 diabetes) at both baseline and follow-up. Furthermore, no exercise duration was assessed; hence, inference was made purely based on exercise frequency. Moreover, ICD-10 codes for sex-specific cancers (e.g., prostate and breast cancers) were masked due to the data management policy set forth by the NHIS, so it was not possible to examine such cancers in the present study. The lack of data on diet, which is another behavioural risk marker for noncommunicable diseases¹² is another limitation. Moreover, a sizeable proportion (n=74,931; 14.6%) of individuals were excluded due to the missing information on the covariates. Another limitation is that the measurement methods to assess the covariates were not standardized across the different medical institutes participating in the NHIS-HEALS cohort.

Conclusion

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Individuals who engaged in sweat-inducing exercise around 3-6 times/week (as opposed to every day) generally had the lowest risk of developing myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancers. These findings were generally applicable to different sub-populations as stratified by body mass index, smoking, alcohol consumption, family history of disease, and sex. Public health and lifestyle interventions should promote a moderate level of sweat-inducing exercise as a behavioural strategy for prevention and control of non-communicable diseases in a wider population of East Asians.

Author Contributions

YK designed this study, performed statistical analysis, and drafted an initial version of the manuscript. SJS, SMH and SHJ all contributed to conceptualizing the study idea and developing the analytical plans, and provided assistance with statistical analysis. All authors critically reviewed, approved of the final version of the manuscript, and agreed to be responsible for all facets of this work.

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Conflicts of interest

None declared.

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Patient consent

Not required.

Ethics approval

This research was approved by the Institutional Review Board (4-2017-0051) of the Yonsei University's Severance Hospital in Republic of Korea.

Data sharing statement

Data sharing is not applicable because no informed consent for data sharing was obtained from the participants.

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	Figure Legends
Figur	e 1. A flow diagram. Note: "N" indicates numbers of total observations (i.e. participations)

numbers of unique participants at baseline. Data without missingness and prevalence of major diseases were used to create final analysis datasets for different incident disease

outcomes; while the number of unique participants at baseline is the same for all incident disease outcomes, the total number of observations varied due to the nature of time-updated covariate analyses (i.e. censoring of subsequent time-updated covariates when an incident disease case occurs before the end date of repeated measures). Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million South Korean adults (2002-2015) with the entire South Korean population's health insurance system.

Figure 2. Associations of exercise frequency with various incident cardiovascular disease outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of heart disease, stroke or hypertension (in models for myocardial infarction, stroke and hypertension) or diabetes (in models for Type 2 diabetes), smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million Korean adults (2002-2015) with the entire South Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

Figure 3. Associations of exercise frequency with various incident cancer outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of cancer, smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million South Korean adults (2002-2015) with the entire South Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

Figure 4. Results from assessment of effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequency and each incident disease outcome. Only associations for which the multiplicative interaction terms were statistically significant are presented. Cox regression models with age as the underlying timescale were adjusted for sex [not in models for effect modification by sex], body mass index [not in models for effect modification by body mass index], systolic blood pressure, fasting glucose levels, total cholesterol levels, family history [not in models for effect modification by family history of respective disease] of heart disease/stroke/hypertension (in models for myocardial infarction, stroke and hypertension), diabetes (in models for Type 2 diabetes) or cancer (in models for each cancer), smoking status [not in models for effect modification by smoking status] and alcohol consumption [not in models for effect modification by alcohol consumption]. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. P-values for multiplicative interactions with exercise frequency are as follows; Outcome - hypertension: body mass index (0.049), smoking (<0.001), alcohol consumption (<0.001), family history of cardiovascular disease (0.029) and sex (<0.001); Outcome - lung cancer: body mass index (0.016), and; Outcome - type 2 diabetes: sex (0.012). Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million South Korean adults

(2002-2015) Abbreviatior) with the entire South Korean population's health insurance system. ns: HR – Hazard Ratio; CI – Confidence Intervals
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Table 1. Characteristics of the participants at baseline.

Variables	All (n=257,854)	Exercise frequency				
		None (n=148,284)	1-2 times/week (n=62,923)	3-4 times/week (n=24,836)	5-6 times/week (n=6,676)	Almost everyda (n=15,135)
Sex, %						
Men	50.5%	43.8%	63.3%	57.5%	52.9%	49.6%
Women	49.5%	56.2%	36.7%	42.5%	47.1%	50.4%
Age, years	50.7 (8.7)	51.5 (9.2)	49.0 (7.5)	49.3 (7.5)	49.9 (7.8)	53.5 (9.3)
Body Mass Index, kg ² /m	23.5 (2.8)	23.3 (2.9)	23.6 (2.7)	23.7 (2.6)	23.7 (2.6)	23.7 (2.7)
Systolic blood pressure, mm Hg	116.8 (11.2)	116.6 (11.3)	117.1 (11.0)	116.8 (11.1)	116.8 (11.2)	117.3 (11.3)
Diastolic blood pressure, mm Hg	73.4 (7.9)	73.1 (8.0)	73.8 (7.8)	73.5 (7.9)	73.4 (8.0)	73.4 (7.9)
Fasting glucose levels, mg/dL	90.2 (12.3)	90.1 (12.4)	90.4 (12.2)	89.9 (11.9)	90.2 (12.3)	90.2 (12.4)
Total cholesterol, mg/dL	197.0 (36.7)	196.5 (37.1)	197.7 (36.2)	197.8 (35.9)	197.8 (36.1)	197.4 (36.8)
Family history of heart disease, stroke or hypertension, %	12.2%	10.8%	13.9%	15.9%	16.5%	10.9%
Family history of cancer, %	14.2%	13.1%	15.3%	17.2%	16.6%	14.5%
Family history of diabetes, %	6.3%	5.4%	7.2%	8.5%	9.2%	5.7%
Smoking status, %						
Never	68.1%	71.9%	59.1%	65.2%	68.8%	71.7%
Previously	8.4%	5.8%	12.0%	12.7%	12.5%	8.8%
Currently	23.6%	22.2%	28.9%	22.1%	18.8%	19.5%
Alcohol Consumption, %						
Never	58.4%	64.5%	47.6%	50.5%	52.2%	59.3%
2-3 times/month	16.4%	13.8%	21.3%	19.7%	18.8%	14.1%
1-2 times/week	15.8%	12.4%	22.0%	20.2%	18.1%	14.5%
≥3 times/week	9.5%	9.3%	9.1%	9.5%	10.8%	12.1%
Incident myocardial infarction, n (%)	3,047 (1.2)	1,741 (1.2)	723 (1.1)	276 (1.1)	88 (1.3)	219 (1.4)
Incident stroke, n (%)	16,134 (6.3)	9,689 (6.5)	3,333 (5.3)	1,482 (6.0)	390 (5.8)	1,240 (8.2)
Incident hypertension, n (%)	120,203 (46.6)	65,964 (44.5)	30,623 (48.7)	12,617 (50.8)	3,294 (49.3)	7,705 (50.9)
Incident Type 2 diabetes, n (%)	50,459 (19.6)	27,128 (18.3)	10,666 (6.5)	5,421 (21.8)	1,399 (21.0)	3,285 (21.7)
Incident stomach cancer, n (%)	4,788 (1.9)	2,672 (1.8)	13,226 (21.0)	489 (2.0)	139 (2.1)	328 (2.2)
Incident colon cancer, n (%)	2,711 (1.1)	1,424 (1.0)	1,160 (1.8)	314 (1.3)	90 (1.3)	191 (1.3)
Incident rectum cancer, n (%)	1,494 (0.6)	809 (0.6)	692 (1.1)	154 (0.6)	46 (0.6)	107 (0.7)
Incident lung cancer, n (%)	3,601 (1.4)	2,138 (1.4)	796 (1.3)	307 (1.2)	85 (1.3)	275 (1.8)
Incident liver cancer, n (%)	2,620 (1.0)	1,423 (1.0)	680 (1.1)	263 (1.1)	75 (1.1)	179 (1.2)
Incident pancreas cancer, n (%)	864 (0.3)	483 (0.3)	205 (0.3)	92 (0.4)	24 (0.4)	60 (0.4)
Incident head & neck cancer, n (%)	656 (0.3)	377 (0.3)	144 (0.2)	73 (0.3)	15 (0.2)	47 (0.3)
Incident kidney cancer, n (%)	589 (0.2)	301 (0.2)	153 (0.2)	75 (0.3)	16 (0.2)	44 (0.3)
Incident gallbladder cancer, n (%)	400 (0.2)	219 (0.1)	83 (0.1)	43 (0.2)	16 (0.2)	39 (0.3)
Incident esophagus cancer, n (%)	352 (0.1)	214 (0.1)	75 (0.1)	29 (0.1)	6 (0.09)	28 (0.2)
Median follow-up period, years (interquartile range)	13.0 (12.2, 13.3)	13.0 (12.2, 13.3)	13.0 (12.2, 13.3)	13.0 (12.2, 13.3)	12.7 (12.2, 13.3)	12.6 (12.2, 13.3

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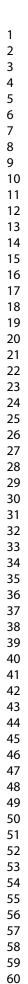
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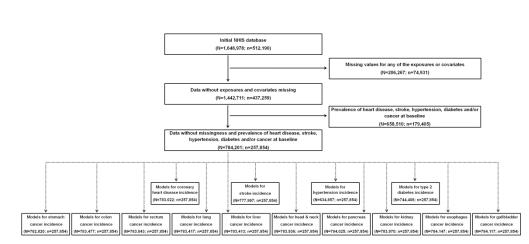


Figure 1. A flow diagram. Note: "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data without missingness and prevalence of major diseases were used to create final analysis datasets for different incident disease outcomes; while the number of unique participants at baseline is the same for all incident disease outcomes, the total number of observations varied due to the nature of time-updated covariate analyses (i.e. censoring of subsequent time-updated covariates when an incident disease case occurs before the end date of repeated measures). Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million South Korean adults (2002-2015) with the entire South Korean population's health insurance system.

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			Total	Unique		Crud
Group		HR (95% CI)	cases(N) participants	s(n) Events(n) rate
Ayocardial infarction						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	1741	40.6
Exercise frequency: 1-2 times/week	→	0.87 (0.80, 0.95)	220601	62923	723	31.7
Exercise frequency: 3-4 times/week	→	0.79 (0.70, 0.90)	92749	24836	276	29.2
Exercise frequency: 5-6 times/week		0.98 (0.79, 1.22)	22457	6676	88	38.2
Exercise frequency: Almost everyday		0.94 (0.82, 1.09)	45038	15135	219	46.4
Stroke						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	9689	232.
Exercise frequency: 1-2 times/week	→	0.86 (0.82, 0.89)	220601	62923	3333	149.
Exercise frequency: 3-4 times/week	→	0.83 (0.79, 0.88)	92749	24836	1482	160.
Exercise frequency: 5-6 times/week	→	0.80 (0.73, 0.89)	22457	6676	390	173.
Exercise frequency: Almost everyday		0.95 (0.90, 1.01)	45038	15135	1240	272
Hypertension						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	65964	238
Exercise frequency: 1-2 times/week	•	0.92 (0.90, 0.93)	220601	62923	30623	211
Exercise frequency: 3-4 times/week	•	0.86 (0.85, 0.88)	92749	24836	12617	207
Exercise frequency: 5-6 times/week	→	0.87 (0.84, 0.90)	22457	6676	3294	219
Exercise frequency: Almost everyday	+	0.95 (0.93, 0.97)	45038	15135	7705	265
Type 2 diabetes						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	27128	145
Exercise frequency: 1-2 times/week	+	0.92 (0.90, 0.94)	220601	62923	13226	167
Exercise frequency: 3-4 times/week	+	0.87 (0.84, 0.89)	92749	24836	5421	174
Exercise frequency: 5-6 times/week	→	0.88 (0.84, 0.93)	22457	6676	1399	168
Exercise frequency: Almost everyday	-	0.97 (0.93, 1.00)	45038	15135	3285	173
	I	1				

Figure 2. Associations of exercise frequency with various incident cardiovascular disease outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of heart disease, stroke or hypertension (in models for myocardial infarction, stroke and hypertension) or diabetes (in models for Type 2 diabetes), smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million Korean adults (2002-2015) with the entire South Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

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Group	HR (95% CI)	cases(N)	participants(n)	Events(n)	
Stomach cancer	1.00 (1.00, 1.00)	403356	148284	2672	
Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week	1.00 (1.00, 1.00) 0.90 (0.84, 0.97)	220601	62923	1160	
Exercise frequency: 3-4 times/week	0.87 (0.79, 0.96)	92749	24836	489	
Exercise frequency: 5-6 times/week	0.93 (0.78, 1.10)	22457	6676	139	
Exercise frequency: Almost everyday	0.88 (0.78, 0.98)	45038	15135	328	
Colon cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	1424	
Exercise frequency: 1-2 times/week	1.05 (0.95, 1.15)	220601	62923	692	
Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week	1.06 (0.93, 1.20) 1.14 (0.92, 1.41)	92749 22457	24836 6676	314 90	
Exercise frequency: Almost everyday	0.97 (0.83, 1.12)	45038	15135	191	
Rectum cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	809	
Exercise frequency: 1-2 times/week	0.96 (0.85, 1.09)	220601	62923	378	
Exercise frequency: 3-4 times/week	0.88 (0.74, 1.05)	92749	24836	154	
Exercise frequency: 5-6 times/week	1.00 (0.74, 1.35) 0.95 (0.78, 1.16)	22457 45038	6676 15135	46 107	
Lung cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	2138	
Exercise frequency: 1-2 times/week	0.90 (0.83, 0.98)	220601	62923	796	
Exercise frequency: 3-4 times/week	0.80 (0.71, 0.91)	92749	24836	307	
Exercise frequency: 5-6 times/week	0.81 (0.65, 1.01)	22457 45038	6676 15135	85 275	
Exercise frequency: Almost everyday	0.93 (0.82, 1.05)	45038	15135	275	
Liver cancer Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	1423	
Exercise frequency: 1-2 times/week	0.95 (0.87, 1.05)	220601	62923	680	
Exercise frequency: 3-4 times/week	0.85 (0.75, 0.98)	92749	24836	263	
Exercise frequency: 5-6 times/week	0.94 (0.74, 1.18)	22457	6676	75	
Exercise frequency: Almost everyday	0.93 (0.79, 1.08)	45038	15135	179	
Pancreas cancer					
Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week	1.00 (1.00, 1.00) 1.02 (0.86, 1.20)	403356 220601	148284 62923	483 205	
Exercise frequency: 3-4 times/week	1.01 (0.81, 1.27)	92749	24836	92	
Exercise frequency: 5-6 times/week	→ 0.97 (0.64, 1.46)	22457	6676	24	
Exercise frequency: Almost everyday	0.92 (0.70, 1.20)	45038	15135	60	
Head&Neck cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	377	
Exercise frequency: 1-2 times/week	0.76 (0.63, 0.93)	220601	62923	144	
Exercise frequency: 3-4 times/week	 0.92 (0.71, 1.19) 0.73 (0.43, 1.22) 	92749 22457	24836 6676	73 15	
Exercise frequency: Almost everyday	- 0.73 (0.43, 1.22) - 0.92 (0.68, 1.25)	45038	15135	47	
Kidney cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	301	
Exercise frequency: 1-2 times/week	0.95 (0.78, 1.17)	220601	62923	153	
Exercise frequency: 3-4 times/week	→ 1.10 (0.85, 1.42) → 0.93 (0.56, 1.54)	92749 22457	24836 6676	75 16	
Exercise frequency: 5-6 times/week	→ 0.93 (0.56, 1.54) → 1.11 (0.81, 1.52)	45038	15135	44	
Gallbladder cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	219	
Exercise frequency: 1-2 times/week	0.98 (0.75, 1.27)	220601	62923	83	
Exercise frequency: 3-4 times/week	1.09 (0.78, 1.52)	92749	24836	43	
Exercise frequency: 5-6 times/week	→ 1.47 (0.88, 2.45)	22457	6676	16	
Exercise frequency: Almost everyday	→ 1.30 (0.93, 1.84)	45038	15135	39	
Esophagus cancer Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	214	
Exercise frequency: 1-2 times/week	0.86 (0.65, 1.12)	220601	62923	75	
Exercise frequency: 3-4 times/week	0.78 (0.52, 1.15)	92749	24836	29	
Exercise frequency: 5-6 times/week	— 0.57 (0.25, 1.29)	22457	6676	6	
Exercise frequency: Almost everyday	→ 0.90 (0.60, 1.33)	45038	15135	28	
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Figure 3. Associations of exercise frequency with various incident cancer outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of cancer, smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million South Korean adults (2002-2015) with the entire South Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

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			Total	Unique		Cru
Group		HR (95% CI)	cases(N)	Unique participants(n)	Events(n)) rat
Hypertension: Non-obese (BMI-25) Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Atimost everyday	*	$\begin{array}{c} 1.00 & (1.00, \ 1.00) \\ 0.92 & (0.91, \ 0.94) \\ 0.85 & (0.83, \ 0.87) \\ 0.86 & (0.82, \ 0.90) \\ 0.95 & (0.92, \ 0.98) \end{array}$	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	23 21 20 21 26
Hypertension: Obese (BMI≥25) Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 2-4 times/week Exercise frequency: 6-6 times/week Exercise frequency: 6-6 timest everyday	≠ _	1.00 (1.00, 1.00) 0.93 (0.90, 0.95) 0.91 (0.88, 0.94) 0.92 (0.87, 0.98) 0.98 (0.94, 1.02)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	231 221 221 221
Hypertension: Smoking - Never Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 2-4 times/week Exercise frequency: 6-6 times/week Exercise frequency: 6-6 timest everyday	* *	$\begin{array}{c} 1.00 & (1.00, 1.00) \\ 0.89 & (0.88, 0.91) \\ 0.82 & (0.81, 0.84) \\ 0.86 & (0.82, 0.89) \\ 0.93 & (0.90, 0.95) \end{array}$	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	231 221 221 201
Hypertension: Smoking - Previously Exercise frequency: Nore (Referênce) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Amost everyday	_ ≠	1.00 (1.00, 1.00) 0.91 (0.87, 0.95) 0.88 (0.83, 0.93) 0.87 (0.79, 0.96) 0.96 (0.88, 1.04)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	221222
Hypertension: Smoking - Currently Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 6-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.98 (0.95, 1.01) 0.97 (0.93, 1.01) 0.95 (0.88, 1.03) 1.03 (0.97, 1.09)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	22222
Hypertension: Alcohol consumption - Never Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 6-6 times/week Exercise frequency: Almost everyday	* _	$\begin{array}{c} 1.00 & (1.00, 1.00) \\ 0.90 & (0.88, 0.92) \\ 0.84 & (0.81, 0.86) \\ 0.84 & (0.80, 0.88) \\ 0.93 & (0.90, 0.96) \end{array}$	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	22222
Hypertension: Alcohol consumption - 2-3 imes/month Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 2-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	+++++++++++++	1.00 (1.00, 1.00) 0.92 (0.89, 0.96) 0.84 (0.80, 0.88) 0.91 (0.84, 0.99) 1.01 (0.95, 1.08)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	222222
Hypertension: Alcohol consumption - 1-2 times/week Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	_ ₹	1.00 (1.00, 1.00) 0.91 (0.88, 0.94) 0.91 (0.87, 0.95) 0.91 (0.84, 0.99) 0.96 (0.91, 1.03)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	22222
Hypertension: Alcohol consumption - 23 times/week Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 2-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		$\begin{array}{c} 1.00 & (1.00, 1.00) \\ 0.98 & (0.94, 1.02) \\ 0.92 & (0.87, 0.97) \\ 0.93 & (0.85, 1.03) \\ 0.99 & (0.92, 1.05) \end{array}$	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	222222
Hypertension: Men Exercise frequency: 1-2 times/week Exercise frequency: 2-1 times/week Exercise frequency: 2-6 times/week Exercise frequency: 6-6 timest everyday		1.00 (1.00, 1.00) 0.94 (0.93, 0.96) 0.92 (0.90, 0.94) 0.93 (0.88, 0.97) 1.00 (0.97, 1.03)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	222222
Hypertension: Women Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 6-6 times/week Exercise frequency: 6-6 timest everyday	* *	1.00 (1.00, 1.00) 0.87 (0.85, 0.89) 0.79 (0.76, 0.81) 0.82 (0.78, 0.87) 0.91 (0.88, 0.95)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	22222
Type 2 diabetes: Men Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 6-6 times/week Exercise frequency: Amost everyday	*	1.00 (1.00, 1.00) 0.91 (0.89, 0.94) 0.87 (0.84, 0.90) 0.88 (0.82, 0.94) 0.93 (0.88, 0.98)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	27128 13226 5421 1399 3285	14
Type 2 diabetes: Women Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 2-4 times/week Exercise frequency: 6-6 times/week Exercise frequency: 6-6 timest everyday	≠ +	1.00 (1.00, 1.00) 0.91 (0.88, 0.95) 0.86 (0.82, 0.90) 0.90 (0.83, 0.98) 1.03 (0.97, 1.08)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	27128 13226 5421 1399 3285	

Figure 4. Results from assessment of effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequency and each incident disease outcome. Only associations for which the multiplicative interaction terms were statistically significant are presented. Cox regression models with age as the underlying timescale were adjusted for sex [not in models for effect modification by sex], body mass index [not in models for effect modification by body mass index], systolic blood pressure, fasting glucose levels, total cholesterol levels, family history [not in models for effect modification by family history of respective disease] of heart disease/stroke/hypertension (in models for myocardial infarction, stroke and hypertension), diabetes (in models for Type 2 diabetes) or cancer (in models for each cancer), smoking status [not in models for effect modification by smoking status] and alcohol consumption [not in models for effect modification by alcohol consumption]. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. P-values for multiplicative interactions with exercise frequency are as follows; Outcome hypertension: body mass index (0.049), smoking (<0.001), alcohol consumption (<0.001), family history of cardiovascular disease (0.029) and sex (<0.001); Outcome - lung cancer: body mass index (0.016), and; Outcome - type 2 diabetes: sex (0.012) - - - - Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million South Korean adults (2002-

2015) with the entire South Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

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Incident disease outcome	Definition
Myocardial infarction	ICD 10 codes I21-I23
Stroke	ICD 10 codes I60-I64
Hypertension	ICD 10 codes I10, I11 and I15, systolic blood pressure ≥140 m
Type 2 diabetes	Hg, diastolic blood pressure ≥90 mm Hg, or physician diagnosi ICD 10 codes E11, fasting glucose ≥126 mg/dL, or physician
ype z diabeles	diagnosis
Stomach cancer	ICD 10 codes C16
Colon cancer	ICD 10 codes C18
Rectum cancer	ICD 10 codes C20
Lung cancer	ICD 10 codes C34 ICD 10 codes C22
Liver cancer Pancreas cancer	ICD 10 codes C22
Head & neck cancer	ICD 10 codes C02-C06, C09-C14 and C32
Kidney cancer	ICD 10 codes C64
Gallbladder cancer	ICD 10 codes C23
Esophagus cancer	ICD 10 codes C15
Abbreviations: ICD – International C	Jassingation of Disease

Repeat	Variables	All	Exercise		cted by copyright, includ	36/bmiopen-2018-025590	
visit 1 st		(n=215,295)	frequency None (n=112,156)	1-2 times/week (n=57,777)	3-4 times/Seek (n=25,390	5-6 3 times/week	Almost everyday (n=13,529
	Sex, %				S II I	a	(
	Men	51.1%	45.0%	61.8%	55.3% 5 6 44.7% 9 6 51.3 (7.5) 6	5 50.6%	48.8%
	Women	48.9%	55.0%	38.2%	<u>44.7% 🕰 🤤 </u>	8 49.4%	51.2%
	Age, years	52.7 (8.6)	53.6 (9.2)	50.9 (7.4)	51.3 (7.5) 5 6	52.3 (8.0)	55.6 (9.1)
	Body Mass Index, kg ² /m	23.5 (2.8)	23.4 (2.9)	23.6 (2.7)	23.7 (2.6)	23.6 (2.6)	23.7 (2.7)
	Systolic blood pressure, mm Hg Diastolic blood pressure, mm Hg	<u>120.5 (14.4)</u> 75.7 (9.9)	120.6 (14.7) 75.6 (9.9)	<u>120.4 (13.9)</u> 75.9 (9.8)	120.0 (13.6) 12 75.5 (9.8) 6 0	3 119.0 (13.9) 5 75.2 (0.9)	<u>121.4 (14</u> 75.7 (9.8)
	Fasting glucose levels, mg/dL	92.6 (18.5)	92.6 (18.8)	92.7 (17.4)	75.5 (9.6) 0 0		93.3 (20.2
	Total cholesterol, mg/dL	197.3 (36.2)	197.0 (36.8)	197.3 (35.6)	92.4 (17.8) +	$\frac{1}{2}$ $\frac{92.0(21.0)}{197.4(35.9)}$	197.8 (36
	Family history of heart disease, stroke or hypertension, %	12.6%	10.7%	14.2%	16.7% deu	16.7% 16.7%	12.0%
	Family history of cancer, %	14.3%	12.7%	15.5%	17.4% 5	6 19.2%	14.5%
	Family history of diabetes, %	6.0%	5.0%	6.7%	8.2% 3 🖫	9.0% 71.7%	5.8%
	Smoking status, %				ini S		
	Never	70.7%	74.8%	62.4%	68.9% Z .	71.7%	74.8%
	Previously	8.6%	5.8%	11.9%	12.4%	11.9%	8.8%
	Currently	20.8%	19.4%	25.7%		16.3%	16.4%
	Alcohol Consumption, %	50.00/	00.00/	10.00/	0	54.000	04.00/
	Never	59.8%	66.9%	49.2%		54.9%	61.8%
	2-3 times/month 1-2 times/week	<u>15.6%</u> 15.8%	12.7% 11.8%	20.5% 21.7%	18.6% 5 19.9%	18.2% 17.0%	12.8% 14.8%
	≥3 times/week	8.8%	8.7%	8.6%	8.7%	10.0%	10.6%
					ologie	om/ on June 8. 2025 at Agence Bibliographique de l	

Sex, % (n=4,7) Men 54.2% 47.0% 64.6% 57.9% 53.8% Women 45.8% 53.0% 35.4% 42.1% 20.0% 53.8% Age, years 53.3 (8.3) 54.2 (8.9) 51.7 (7.2) 52.3 (7.4) 53.4 (2.8) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6)	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	(n=73,660) (n=44,211) (n=19,593) 1 times/week eve Sex, % (n=4,711) (n=4,771) (n=4,771) (n=4,771) Men 54.2% 47.0% 64.6% 57.9% 53.8% 53.3 Women 45.8% 53.0% 35.4% 42.1% 46.2% 46.3% Age, years 53.3 (8.3) 54.2 (8.9) 51.7 (7.2) 52.3 (7.4) 53.4 (7.8) 56.4 Body Mass Index, kg ² /m 23.5 (2.7) 23.4 (2.8) 23.6 (2.6) 23.7 (2.6) 120.3 (13.7) 122 Diastolic blood pressure, mm Hg 75.8 (9.6) 75.8 (9.7) 76.0 (9.5) 75.5 (9.4) 6 93.2 (15.9) 93.1 (17.4) 93.5 (17.0) 93.1 (15.5) 197.4 (35.4) 197.7 (36.5) 197.4 (35.4) 197.7 (36.5) 197.4 (35.4) 197.8 (35.8) 6 18.3% 13.3 Total cholesterol, mg/dL 19.7% (35.5) 197.4 (35.4) 197.7 (36.5) 197.4 (35.4) 197.7 (36.5) 197.4 (35.4) 197.7 (36.5) 197.4 (35.4) 197.7 (36.5) 197.4 (35.4) 197.7 (36.5) 197.4 (35.4) 197.7 (36.5) 197.4 (35.4) 197.7 (36.5) 197.4 (35.4) </th
Men 54.2% 47.0% 64.6% 57.9% 53.8% Women 45.8% 53.0% 35.4% 42.1% Eg b 66.2% Age, years 53.3 (8.3) 54.2 (8.9) 51.7 (7.2) 52.3 (7.4) Greet 53.4 (2.8) Body Mass Index, kg²/m 23.5 (2.7) 23.4 (2.8) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6) Systolic blood pressure, mm Hg 120.9 (14.1) 121.0 (14.5) 120.7 (13.7) 120.4 (13.6) 23.6 (2.6) Fasting glucose levels, mg/dL 93.2 (16.9) 93.1 (17.4) 93.5 (17.0) 93.1 (15.5) 197.4 (35.4) 197.8 (35.4) 196.7 Family history of heart disease, stroke or hypertension, % 13.4% 11.2% 14.6% 17.5% 0.6 196.7 196.7 196.7 196.7 197.4 (35.4) 197.8 (35.2) 197.7 (36.5) 197.4 (35.4) 197.8 (35.4) 196.7 196.7 196.7 196.7 196.7 196.7 196.7 196.7 196.7 196.7 196.7 196.7 196.7 196.7 196.7 196.7 196.7	47.0% $64.6%$ $57.9%$ 56.5 $53.8%$ 53.3 $53.0%$ $35.4%$ $42.1%$ 90.5 $53.8%$ 53.3 54.2 (8.9) 51.7 (7.2) 52.3 (7.4) 53.4 (7.8) 56.3 23.4 (2.8) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6) 23.6 121.0 (14.5) 120.7 (13.7) 120.4 (13.6) 120.3 (13.7) 122 75.8 (9.7) 76.0 (9.5) 75.5 (9.4) $6.5%$ 75.4 (9.4) 76.0 93.1 (17.4) 93.5 (17.0) 93.1 (15.5) 93.5 (15.9) 93.3 197.7 (36.5) 197.4 (35.4) 197.8 (35.4) 93.5 (15.9) 93.3 197.7 (36.5) 197.4 (35.4) 197.8 (35.4) 93.5 (15.9) 93.5 13.7 $12.9%$ $16.4%$ $17.5%$ $18.3%$ 13.1 $13.1%$ $13.1%$ $13.1%$ $13.1%$ $13.1%$ $9.0%$ $61.4%$ $76.5%$ $62.3%$ $68.7%$ $71.2%$ 74.2 74.2 74.2 74.2 74.2 74.2 74.2 74.2 74.2	Men 54.2% 47.0% 64.6% 57.9% 53.8% 53.4 Women 45.8% 53.0% 35.4% 42.1% 46.2% 46.3 Age, years 53.3 (8.3) 54.2 (8.9) 51.7 (7.2) 52.3 (7.4) 46.2% 46.3 Body Mass Index, kg ² /m 23.5 (2.7) 23.4 (2.8) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6) 23.6 (2.6) 23.1 (7.8) 55.4 (7.8) 55.4 (7.8) 55.4 (7.8) 55.4 (7.8) 53.4 (7.8) 56.4 53.4 (7.8) <t< th=""></t<>
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Body Mass Index, kg²/m 23.5 (2.7) 23.4 (2.8) 23.6 (2.6) 23.7 (2.6) 23.7 (2.6) 23.6 (2.7) 23.4 (2.8) 23.6 (2.6) 23.7 (2.6) 23.6 (2.7) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6) 23.7 (2.6) 23.6 (2.7) 23.6 (2.6) 23.7 (2.6) 23.6 (2.7) 120.4 (13.6) 23.6 (2.7) 120.4 (13.6) 23.6 (2.7) 120.4 (13.6) 23.6 (2.6) 23.7 (2.6) 23.7 (2.6) 23.7 (2.6) 23.7 (2.6) 23.7 (2.6) 23.7 (2.6) 23.6 (2.6) 23.7 (2.6) 23.7 (2.6) 23.6 (2.6) 23.7 (2.6) 23.7 (2.6) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6) 120.7 (13.7) 120.4 (13.6) 120.7 (13.7) 120.4 (13.6) 120.7 (13.7) 120.4 (13.6) 120.7 (13.7) 120.4 (13.6) 120.7 (13.7) 130.4 (15.6) 93.7 (17.0) 93.1 (17.4) 93.5 (17.0) 93.1 (15.5) 197.4 (35.4) 197.8 (35.2) 97.4 (35.4) 197.8 (35.2) 97.4 (35.4) 197.8 (35.2) 97.4 (35.4) 197.8 (35.2) 197.4 (35.4) 197.8 (35.2) 197.4 (35.4) 197.8 (35.2) 197.4 (35.4) 197.8 (35.2) 197.4 (35.4) 197.8 (35.2) 197.4 (35.4)	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Body Mass Index, kg²/m 23.5 (2.7) 23.4 (2.8) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6) 23.4 (2.8) Systolic blood pressure, mm Hg 120.9 (14.1) 121.0 (14.5) 120.7 (13.7) 120.4 (13.6) 120.3 (13.7) 122 Diastolic blood pressure, mm Hg 75.8 (9.6) 75.8 (9.7) 76.0 (9.5) 75.5 (9.4) 75.4 (9.4) 76.1 (9.5) Fasting glucose levels, mg/dL 93.2 (16.9) 93.1 (17.4) 93.5 (17.0) 93.1 (15.5) 93.5 (15.9) 93.5 Total cholesterol, mg/dL 197.6 (35.9) 197.7 (36.5) 197.4 (35.4) 197.8 (35.5) 93.5 18.3% 13. hypertension, % 11.2% 14.6% 17.4% 10.7% 15.4 19.7% 15.4 Family history of diabetes, % 6.3% 5.2% 7.1% 8.2% 9.0% 6.1% Smoking status, % 71.0% 76.5% 62.3% 68.7% 71.2% 74.2 Previously 9.0% 5.5% 12.5% 13.1% 13.1% 9.4 Currently 20.0% 18.0% 25.3% 18.2% 13.1% 13.8% 16.6
Body Mass Index, kg²/m 23.5 (2.7) 23.4 (2.8) 23.6 (2.6) 23.7 (2.6) 23.6 (2.7) Systolic blood pressure, mm Hg 120.9 (14.1) 121.0 (14.5) 120.7 (13.7) 120.4 (13.6) 72.4 (13.6) Diastolic blood pressure, mm Hg 75.8 (9.6) 75.8 (9.7) 76.0 (9.5) 75.5 (9.4) 93.5 (17.0) 93.1 (15.5) 93.5 (17.0) 93.1 (15.5) 93.5 (17.0) 93.1 (15.5) 93.5 (17.0) 93.1 (15.5) 97.4 (35.4) 197.8 (35.2) 93.5 (17.0) 93.1 (15.5) 197.4 (35.4) 197.8 (35.2) 197.7 (36.5) 197.4 (35.4) 197.8 (35.2) 197.7 (36.5) 197.4 (35.4) 197.8 (35.2) 197.7 (36.5) 197.4 (35.4) 197.8 (35.2) 197.7 (36.5) 197.4 (35.4) 197.8 (35.2) 197.7 (36.5) 197.4 (35.4) 197.8 (35.2) 197.7 (36.5) 197.4 (35.4) 197.8 (35.2) 197.7 (36.5) 197.4 (35.4) 197.8 (35.2) 197.7 (36.5) 197.4 (35.4) 197.8 (35.2) 197.7 (36.5) 197.4 (35.4) 197.8 (35.2) 197.7 (36.5) 197.4 (35.4) 197.8 (35.2) 197.7 (36.5) 197.4 (35.4) 197.8 (35.2) 197.8 (35.2) 197.8 (35.2) 197.8 (35.2) 197.8 (35.2) 197.8 (35.2) 197.8 (35.2) <td< td=""><td>$\begin{array}{c ccccccccccccccccccccccccccccccccccc$</td><td>Body Mass Index, kg²/m 23.5 (2.7) 23.4 (2.8) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6)</td></td<>	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Body Mass Index, kg²/m 23.5 (2.7) 23.4 (2.8) 23.6 (2.6) 23.7 (2.6) 23.6 (2.6)
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Repeat visit	Variables	All (n=80,639)	Exercise frequency		5 4	2018-025590 c	
3 rd			None (n= 36,123)	1-2 times/week (n=26,505)		times/week	Almost everyday (n=4,188)
	Sex, %				lse Be	ייע	
	Men	63.1%	53.9%	73.0%	68.6% S S	64.5%	63.4%
	Women	36.9%	46.1%	27.0%	31.4% ഇ !	2 35.6%	36.7%
	Age, years	52.3 (7.2)	52.9 (7.8)	51.2 (6.2)	51.9 (6.6) 2 6	52.8 (7.0)	55.2 (8.4)
	Body Mass Index, kg²/m 🛛 🦯 🚬 👝	23.5 (2.7)	23.3 (2.8)	23.6 (2.6)	23.7 (2.5) č 3	23.7 (2.6)	23.7 (2.7)
	Systolic blood pressure, mm Hg	121.1 (13.6)	120.9 (13.9)	120.9 (13.4)	121.0 (13. ð) 🕺	120.6 (13.3)	122.0 (14.
	Diastolic blood pressure, mm Hg	76.1 (9.4)	76.0 (9.5)	76.4 (9.4)	76.1 (9.1) 6 0 93.9 (15.9) 6 5	5 75.6 (9.5)	76.3 (9.6)
	Fasting glucose levels, mg/dL	93.7 (16.8)	93.3 (17.1)	94.1 (16.7)	93.9 (15.9) - 5	94.1 (16.5)	94.5 (17.0
	Total cholesterol, mg/dL	197.1 (35.2)	197.1 (35.5)	197.4 (34.8)	196.9 (34. 2) q	196.5 (35.2)	196.7 (35.
	Family history of heart disease, stroke or hypertension, %	13.5%	11.4%	14.8%	196.9 (34. 4) er 16.7% der 17.8% a A	18.6%	11.7%
	Family history of cancer, %	14.8%	13.0%	15.8%	17.8% 🖬 🔁	<u>18.9%</u>	14.7%
	Family history of diabetes, %	6.4%	5.3%	7.0%	<u>9</u> /0/2	S 0 50/.	6.2%
	Smoking status, %				63.9% g.		
	Never	66.6%	73.8%	57.6%	63.9% д .	65.5%	68.8%
	Previously	10.7%	6.1%	14.0%	15.5%	16.6%	12.4%
	Currently	22.8%	20.2%	28.4%		3 17.9%	18.7%
	Alcohol Consumption, %				<u> </u>	2	
	Never	53.6%	64.2%	42.5%		47.4%	53.9%
	2-3 times/month	18.5%	14.0%	23.7%	20.8%	21.4%	15.8%
	1-2 times/week	19.5%	14.0%	25.6 %	22.8%	20.7%	18.8%
	≥3 times/week	8.4%	7.8%	8.3%	9.2% an	10.5%	11.5%
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4 th None 1-2 times/week 3-4 times/week 5-6 Aln Sex, % (n=1,624) (n=5,685) times/week eve Men 72.3% 61.6% 81.1% 81.5% 76.2% 73.3 Women 27.7% 38.4% 18.9% 18.5% 76.2% 73.2% Age, years 50.9 (5.4) 51.2 (5.5) 50.6 (5.1) 50.7 (5.3) 51.0 (5.6) 52.2 Body Mass Index, kg ² /m 23.5 (2.7) 23.3 (2.7) 23.7 (2.6) 23.8 (2.6) 23.8 (2.5) 23.8 (2.5) 23.8 (2.5) 23.8 (2.6) 23.8 (Repeat visit	Variables	All (n=40,910)	Exercise frequency		cted by copyright, includi	7 0 0	
Sex, % 72.3% 61.6% 81.1% 81.5% 78.2% 73.2% Women 27.7% 38.4% 18.9% 18.5% 78.2% 73.2% 73.2% Age, years 50.9 (5.4) 51.2 (5.5) 50.6 (5.1) 50.7 (5.3) 76.2% 21.9% 26. Body Mass Index, kg²/m 23.5 (2.7) 23.3 (2.7) 23.7 (2.6) 23.8 (2.6) 23.8 (2.5) 24.3 % 24.3 % 23.8 (2.5) 23.8 (2.5) 24.3 % 24.3 % 24.3 % 24.3 %			(- /)	None		(n= 5,685) o	times/week	Alm eve (n=
Men 72.3% 61.6% 81.1% 81.5% 65 78.2% 73.3% Women 27.7% 38.4% 18.9% 18.5% 65 78.2% 73.3% Age, years 50.9 (5.4) 51.2 (5.5) 50.6 (5.1) 50.7 (5.3) 65 21.9% 23.5 Body Mass Index, kg ² /m 23.5 (2.7) 23.3 (2.7) 23.7 (2.6) 23.8 (2.6) 23.8 (2.5) 23.8 Systolic blood pressure, mm Hg 76.6 (9.2) 76.2 (9.3) 77.0 (9.2) 76.8 (9.4) 77.7 Fasting glucose levels, mg/dL 93.9 (17.8) 93.3 (17.9) 94.4 (17.9) 94.3 (17.1 F 94.0 (16.0) 94. Total cholesterol, mg/dL 196.8 (35.0) 197.2 (35.5) 196.7 (34.6) 196.6 (34.42) 94.0 (16.0) 94. Family history of cancer, % 13.8% 12.6% 14.7% 15.0% 67.5% 67.5% 67.5% 67.5% 67.5% 67.5% 67.5% 67.5% 67.5% 67.5% 67.5% 67.5% 67.5% 67.5% 67.5% 67.5% 67.5% </td <td></td> <td>Sex, %</td> <td></td> <td></td> <td></td> <td></td> <td>2</td> <td>(</td>		Sex, %					2	(
Women 27.7% 38.4% 18.9% 18.5% 16.5% 21.9% 26. Age, years 50.9 (5.4) 51.2 (5.5) 50.6 (5.1) 50.7 (5.3) 51.0 (5.6) 52. Body Mass Index, kg²/m 23.5 (2.7) 23.3 (2.7) 23.3 (2.7) 23.3 (2.5) 23.8 (2.5) </td <td></td> <td></td> <td></td> <td></td> <td></td> <td>81.5%</td> <td>78.2%</td> <td>73.9</td>						81.5%	78.2%	73.9
Body Mass Index, kg/m 23.5 (2.7) 23.3 (2.7) 23.7 (2.6) 23.8 (2.6) • • • • • • • • • • • • • • • • • • •						18.5% 🖳 🖸 	21.9%	26.1
Systolic blood pressure, mm Hg 121.4 (13.3) 120.9 (13.5) 121.7 (13.0) 121.5 (12.6) 2 121.5 (13.1) 122 Diastolic blood pressure, mm Hg 76.6 (9.2) 76.2 (9.3) 77.0 (9.2) 76.8 (8.9) 77.8 (9.4) 77. Fasting glucose levels, mg/dL 93.9 (17.8) 93.3 (17.9) 94.4 (17.9) 94.3 (17.1) 94.9 (16.0) 94.9 Total cholesterol, mg/dL 196.8 (35.0) 197.2 (35.5) 196.7 (34.6) 196.6 (34.2) 96.9 (34.3) 199 Family history of heart disease, stroke or hypertension, % 12.3% 10.4% 13.7% 14.2% 66.6 16.3% 11. Family history of cancer, % 5.7% 4.8% 6.2% 6.9% 16.3% 13.8 12.6% 14.7% 15.0% 16.3% 13.8% 12.6% 14.7% 15.0% 6.7% 6.7% 6.9% 16.3% 13.8% 12.6% 14.7% 15.0% 6.7% <td></td> <td>Age, years</td> <td></td> <td></td> <td></td> <td>50.7 (5.3) 5 e</td> <td>51.0 (5.6)</td> <td></td>		Age, years				50.7 (5.3) 5 e	51.0 (5.6)	
Diastolic blood pressure, mm Hg 76.6 (9.2) 76.2 (9.3) 77.0 (9.2) 76.8 (8.9) to get 76.8 (9.4) 77. Fasting glucose levels, mg/dL 93.9 (17.8) 93.3 (17.9) 94.4 (17.9) 94.3 (17.11, 14, 54, 54, 94.0 (16.0) 94. Total cholesterol, mg/dL 196.8 (35.0) 197.2 (35.5) 196.7 (34.6) 196.6 (34.21, 94, 64, 64, 74, 74, 74, 75, 75, 74, 74, 74, 74, 74, 74, 75, 75, 74, 74, 74, 74, 74, 74, 74, 74, 74, 74							23.8 (2.5)	
Fasting glucose levels, mg/dL 93.9 (17.8) 93.3 (17.9) 94.4 (17.9) 94.3 (17.1) 94.9 94.0 (16.0) 94. Total cholesterol, mg/dL 196.8 (35.0) 197.2 (35.5) 196.7 (34.6) 196.6 (34.9) 94.9 195.0 (34.3) 196.8 (35.0) 197.2 (35.5) 196.7 (34.6) 196.6 (34.9) 94.9 195.0 (34.3) 196.8 (35.0) 197.2 (35.5) 196.7 (34.6) 196.6 (34.9) 94.9 195.0 (34.3) 196.8 (35.0) 197.2 (35.5) 196.7 (34.6) 196.6 (34.9) 94.0 (16.0) 94.1 (17.9) 94.3 (17.1) 196.8 (34.9) 195.0 (34.3) 196.8 (35.0) 197.2 (35.5) 196.7 (34.6) 196.6 (34.9) 99.0 (34.3) 196 Main of the part disease, stroke or hypertension, % 12.3% 10.4% 13.7% 14.2% 0 0 0 16.3% 11. Family history of diabetes, % 5.7% 4.8% 6.2% 6.9% 15.7% 6.7 55.5% 9 7.5% 6.7 Smoking status, % 12.2% 6.9% 15.1% 18.7% 18.7% 15.7% 12.7% 62.7% 23.0% 24.0% 22. Alcohol Consumption, %							<u>121.5 (13.1)</u>	
Family history of cancer, % 13.8% 12.6% 14.7% 15.0% a ≥ 0 16.3% 13. Family history of diabetes, % 5.7% 4.8% 6.2% 6.9% 3000 7.5% 6.7 Smoking status, %							76.8 (9.4)	
Family history of cancer, % 13.8% 12.6% 14.7% 15.0% a ≥ 0 16.3% 13. Family history of diabetes, % 5.7% 4.8% 6.2% 6.9% 3000 7.5% 6.7 Smoking status, %						<u>94.3 (17.1)</u> 106.6 (24 9) 0 0	94.0(10.0)	
Family history of cancer, % 13.8% 12.6% 14.7% 15.0% a ≥ 0 16.3% 13.8% Family history of diabetes, % 5.7% 4.8% 6.2% 6.9% 3000 7.5% 6.7 Smoking status, % 57.3% 60.6% 69.5% 51.9% 55.5% 57.3% 62. Never 60.6% 69.5% 51.9% 55.5% 57.3% 62. Currently 12.2% 6.9% 15.1% 18.7% 15. Currently 27.2% 23.7% 33.0% 25.8% 24.0% 22. Alcohol Consumption, % 39.9% 45. 2-3 times/month 20.5% 15.5% 24.9% 24.3% 24.0% 19. 1-2 times/week 22.4% 16.2% 28.4% 26.3% 22.6% 22. ≥3 times/week 9.0% 8.2% 8.7% 10.3% 13.6% 12.		Family history of heart disease, stroke or			· · · ·	14.2% dec d	16.3%	11.6
Family history of diabetes, % 5.7% 4.8% 6.2% 6.9% ■ ■ 3 7.5% 6.7 Smoking status, %			13.8%	12.6%	14.7%	15.0% DC	16.3%	13.5
Never 60.6% 69.5% 51.9% 55.5% 57.3% 62. Previously 12.2% 6.9% 15.1% 18.7% 15. Currently 27.2% 23.7% 33.0% 25.8% 24.0% 22. Alcohol Consumption, % 48.1% 60.0% 38.0% 39.1% 39.9% 45. 2-3 times/month 20.5% 15.5% 24.9% 24.3% 22.6% 22. 1-2 times/week 22.4% 16.2% 28.4% 26.3% 22.6% 22. ≥3 times/week 9.0% 8.2% 8.7% 10.3% 13.6% 12.						6.9% 3 🖫	7.5%	6.79
Never 60.6% 69.5% 51.9% 55.5% 57.3% 62. Previously 12.2% 6.9% 15.1% 18.7% 15. Currently 27.2% 23.7% 33.0% 25.8% 24.0% 22. Alcohol Consumption, % 48.1% 60.0% 38.0% 39.1% 39.9% 45. 2-3 times/month 20.5% 15.5% 24.9% 24.3% 22.6% 22. 1-2 times/week 22.4% 16.2% 28.4% 26.3% 22.6% 22. ≥3 times/week 9.0% 8.2% 8.7% 10.3% 13.6% 12.								
Currently 27.2% 23.7% 33.0% 25.8% 24.0% 22. Alcohol Consumption, % 38.0% 39.1% 39.9% 45. Never 48.1% 60.0% 38.0% 39.1% 39.9% 45. 2-3 times/month 20.5% 15.5% 24.9% 24.3% 24.0% 19. 1-2 times/week 22.4% 16.2% 28.4% 26.3% 22.6% 22. ≥3 times/week 9.0% 8.2% 8.7% 10.3% 13.6% 12.		Never	60.6%	69.5%		55.5%	57.3%	62.0
Alcohol Consumption, % 38.0% 39.1% 39.9% 45. 2-3 times/month 20.5% 15.5% 24.9% 24.3% 24.0% 19. 1-2 times/week 22.4% 16.2% 28.4% 26.3% 22.6% 22. ≥3 times/week 9.0% 8.2% 8.7% 10.3% 13.6% 12.								15.7
Never 48.1% 60.0% 38.0% 39.1% 39.9% 45. 2-3 times/month 20.5% 15.5% 24.9% 24.3% 24.0% 19. 1-2 times/week 22.4% 16.2% 28.4% 26.3% 22.6% 22. ≥3 times/week 9.0% 8.2% 8.7% 10.3% 13.6% 12.			27.2%	23.7%	33.0%			22.4
2-3 times/month 20.5% 15.5% 24.9% 24.3% 2 24.0% 19. 1-2 times/week 22.4% 16.2% 28.4% 26.3% 22.6% 22. ≥3 times/week 9.0% 8.2% 8.7% 10.3% 13.6% 12.						<u> </u>		
1-2 times/week 22.4% 16.2% 28.4% 26.3% 22.6% 22. ≥3 times/week 9.0% 8.2% 8.7% 10.3% 13.6% 12.								
≥3 times/week 9.0% 8.2% 8.7% 10.3% 5 5 13.6% 12.								
<u>2 3</u>								
similar techno		≥3 times/week	9.0%	8.2%	8.7%	<u>a</u>	13.6%	12.0
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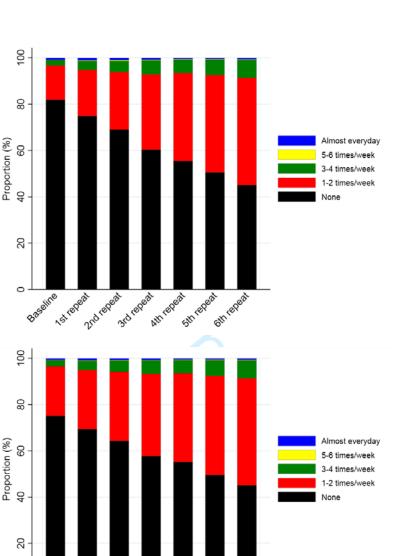
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Repeat	Variables	All	Exercise		cted by copyright, includi		
visit 5 th		(n= 26,356)	frequency None (n=10,771)	1-2 times/week (n=9,807)	3-4 times/week	5-6 times/week	Almost everyday (n=1,170)
	Sex, %				se		(1=1,170)
	Men	73.7%	62.6%	81.6%	82.4%	81.2%	76.9%
	Women	26.3%	37.4%	18.4%	17.6% e.g 51.0 (4.7) te e	18.8%	23.0%
	Age, years	51.1 (4.9)	51.4 (5.1)	50.8 (4.7)	51.0 (4.7)	51.4 (5.0)	52.1 (5.6)
	Body Mass Index, kg²/m	23.5 (2.6)	23.3 (2.7)	23.7 (2.6)	23.8 (2.4) a z ·	23.7 (2.5)	23.8 (2.6)
	Systolic blood pressure, mm Hg	121.4 (13.0)	121.0 (13.4)	121.8 (12.9)	121.6 (12.6)		121.5 (12
	Diastolic blood pressure, mm Hg	76.6 (9.1)	76.2 (9.1)	77.1 (9.0)	76.8 (8.8) 6 04 7 (40 0 6	/6./ (8.6)	76.4 (9.0)
	Fasting glucose levels, mg/dL	94.3 (17.6)	93.7 (18.1)	94.6 (17.3)	94.7 (16.6)	94.6 (15.9)	95.4 (18.7
	Total cholesterol, mg/dL Family history of heart disease, stroke or	197.1 (34.5) 12.6%	<u>197.7 (34.8)</u> 11.3%	<u>196.7 (34.2)</u> 13.4%	196.4 (33.8) 9 4 14.3% - 0	132.2 (34.2)	<u>198.2 (37</u> 10.9%
	hypertension, %	12.0%	11.3%	13.470	14.3% 4 6 6	13.0%	10.9%
	Family history of cancer, %	14.3%	13.2%	15.1%	14.9% a D	13.8%	13.5%
	Family history of diabetes, %	5.9%	4.9%	6.4%	6.7% 3 0	7.2%	8.6%
	Smoking status, %					7.2% 57.0%	
	Never	58.9%	68.1%	50.8%	54.4%	57.0%	58.5%
	Previously	13.1% 🧹	7.1%	16.0%	19.3%	19.8%	19.7%
	Currently	28.0%	24.8%	33.2%	26.2%	23.2%	21.9%
	Alcohol Consumption, %						
	Never	46.3%	57.9%	37.6%	38.3% n		42.9%
	2-3 times/month	21.7%	16.7%	25.8%	24.7%	22.2%	22.3%
	1-2 times/week ≥3 times/week	23.4% 8.6%	17.4% 8.1%	28.0% 8.5%	27.3% 9 .8%	26.0% 10.5%	25.0% 9.7%
		0.070	0.170	0	<u> </u>		0.170
					ologies.		
					S. Ar Agenice Dibliographilique de Xhtml		

Repeat Variables visit	All (n= 12,302)	Exercise frequency		ludin	36/hmiopen-2018-025590 o	
6 th		None (n= 4,684)	1-2 times/week (n=4,754)	3-4 times/week (n=1,929) o u	times/week (n=358)	Almo ever (n=5
Sex, %				seg	80.7%	
Men	76.2%	64.2%	83.8%	84.7%	<u>80.7%</u>	80.4
Women	23.8%	35.8%	16.2%	15.3% e.g 51.0 (4.4) e e	<u>19.3%</u>	19.6
Age, years	51.3 (4.5)	51.6 (4.7)	51.0 (4.2)	51.0 (4.4)	<u>51.2 (4.3)</u>	52.0
Body Mass Index, kg ² /m	23.6 (2.6)	23.3 (2.7)	23.7 (2.6)	23.8 (2.4)	23.6 (2.2)	23.7
Systolic blood pressure, mm Hg	121.5 (12.8)	121.2 (13.0)	121.6 (12.6)	121.7 (12.6)	5 121.0 (12.5)	122.
Diastolic blood pressure, mm Hg Fasting glucose levels, mg/dL	76.7 (9.0)	76.4 (9.0)	77.0 (8.9)	77.0 (9.0) 6 0		76.3
Total cholesterol, mg/dL	94.6 (18.5) 197.1 (34.5)	93.7 (18.8) 197.9 (35.0)	95.1 (18.7) 197.1 (34.2)		95.1 (16.4) 102.0 (22.2)	95.7 197
Family history of heart disease, stroke or hypertension, %	13.2%	11.7%	13.7%	94.9 (16.6) + period 195.8 (34.4) - period 15.5% - certain cart	14.3%	12.7
Family history of cancer, %	14.5%	12.9%	15.5%	15.7% birbe	j 15.1%	14.9
Family history of diabetes, %	6.4%	5.5%	6.4%	7.3% 3 🖫	3 7.3%	9.5%
Smoking status, %				n S		
Never	56.9%	66.6%	48.7%	53.6%		57.4
Previously	14.0%	7.0%	17.3%	20.4%	16.8%	21.1
Currently	29.1%	26.5%	34.1%		26.0%	21.5
Alcohol Consumption, %				irai		
Never	43.7%	56.5%	35.0%		40.5%	37.8
2-3 times/month	22.8%	17.0%	27.2%	24.9%	24.6%	24.8
1-2 times/week	24.8%	17.6%	30.0%	28.3%	26.5%	27.4
≥3 times/week	8.8%	8.8%	7.9%	10.4% n	8.4%	10.1
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oom/ on June 8, 2025 at Agence Bibliographique d similar technologies.

del



2nd repeat

1strepeat

Baseline

Athrepeat

5th repeat

3rd repeat

othrepeat

Supplementary Figure 1. Changes in proportions of exercise frequency categories across 7 time points in all 257,854 individuals who provided data at each respective assessment visit (top panel), and 12,302 individuals who provided data from all 7 assessment visits (bottom panel).

P	a	
1		
3 4 5		
6 7 8 9		
1	0 1	
1 1	2 3	
1	4 5	
1 1	6 7	
1	8 9	
2	0	
2	2 3 4	
2 2 2	5 6	
2 2	7 8	
3	9 0	
3	1 2 3	
3	3 4 5	
	6	
3 3	8 9	
4	1	
4 4 4	3	
	5	
4		
4 5	9 0	
5 5	2	
5	3	

Group		HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n	Cruc) rate
Myocardial infarction						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	1741	40.6
Exercise frequency: 1-2 times/week		0.98 (0.90, 1.07)	220601	62923	723	31.7
Exercise frequency: 3-4 times/week	←	0.83 (0.73, 0.94)	92749	24836	276	29.2
Exercise frequency: 5-6 times/week		0.98 (0.79, 1.22)	22457	6676	88	38.2
Exercise frequency: Almost everyday		0.97 (0.84, 1.12)	45038	15135	219	46.4
Stroke						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	9689	232
Exercise frequency: 1-2 times/week	+	0.86 (0.82, 0.89)		62923	3333	149
Exercise frequency: 3-4 times/week	←	0.83 (0.79, 0.88)		24836	1482	160
Exercise frequency: 5-6 times/week	-	0.80 (0.72, 0.88)		6676	390	173
Exercise frequency: Almost everyday		0.95 (0.90, 1.01)	45038	15135	1240	272
Hypertension						
Exercise frequency: None (Reference)	.1	1.00 (1.00, 1.00)		148284	65964	238
Exercise frequency: 1-2 times/week	•	0.98 (0.96, 0.99)		62923	30623	211
Exercise frequency: 3-4 times/week	•	0.90 (0.89, 0.92)		24836	12617	207
Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	+ ↓	0.91 (0.88, 0.94) 1.00 (0.97, 1.02)		6676 15135	3294 7705	219 265
Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	+ + +	1.00 (1.00, 1.00) 1.00 (0.98, 1.02) 0.91 (0.89, 0.94) 0.92 (0.88, 0.97) 1.01 (0.97, 1.04)	220601 92749 22457	148284 62923 24836 6676 15135	27128 13226 5421 1399 3285	145 167 174 168 173
Г .3	1 1	1				

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Group		HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Crud rate
stomach cancer						
Exercise frequency: None (Reference)	•	1.00 (1.00, 1.00)	403356	148284	2672	143.
Exercise frequency: 1-2 times/week	_ + _	1.01 (0.95, 1.09)	220601	62923	1160	146.6
Exercise frequency: 3-4 times/week	-+	0.94 (0.85, 1.03)	92749	24836	489	157.4
Exercise frequency: 5-6 times/week		0.99 (0.83, 1.17)	22457	6676	139	167
Exercise frequency: Almost everyday	_ →]	0.93 (0.83, 1.04)	45038	15135	328	173.5
Colon cancer						
Exercise frequency: None (Reference)	•	1.00 (1.00, 1.00)	403356	148284	1424	76.5
Exercise frequency: 1-2 times/week		1.13 (1.03, 1.24)	220601	62923	692	87.4
Exercise frequency: 3-4 times/week		1.12 (0.99, 1.27)	92749	24836	314	101.1
Exercise frequency: 5-6 times/week	_	 1.20 (0.97, 1.48) 	22457	6676	90	108.2
Exercise frequency: Almost everyday	_ _ `	1.02 (0.87, 1.18)	45038	15135	191	101
Rectum cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	809	43.5
Exercise frequency: 1-2 times/week		1.07 (0.94, 1.21)	220601	62923	378	47.8
Exercise frequency: 3-4 times/week		0.95 (0.80, 1.13)	92749	24836	154	49.6
Exercise frequency: 5-6 times/week		 1.07 (0.79, 1.43) 	22457	6676	46	55.3
Exercise frequency: Almost everyday	` _	1.01 (0.82, 1.23)	45038	15135	107	56.6
ung cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	2138	114.9
Exercise frequency: 1-2 times/week		0.97 (0.89, 1.05)	220601	62923	796	100.6
Exercise frequency: 3-4 times/week	_ → _ `	0.81 (0.72, 0.91)	92749	24836	307	98.8
Exercise frequency: 5-6 times/week		0.80 (0.65, 1.00)	22457	6676	85	102.1
Exercise frequency: Almost everyday	` → +	0.94 (0.83, 1.07)	45038	15135	275	145.4
iver cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	1423	76.5
Exercise frequency: 1-2 times/week	∔ •	1.07 (0.97, 1.17)	220601	62923	680	85.9
Exercise frequency: 3-4 times/week	→ _`	0.91 (0.80, 1.04)	92749	24836	263	84.7
Exercise frequency: 5-6 times/week		0.99 (0.78, 1.24)	22457	6676	75	90.1
Exercise frequency: Almost everyday	-	0.99 (0.84, 1.15)	45038	15135	179	94.7
ancreas cancer						
Exercise frequency: None (Reference)	•	1.00 (1.00, 1.00)	403356	148284	483	26
Exercise frequency: 1-2 times/week	+	1.05 (0.89, 1.24)	220601	62923	205	25.9
Exercise frequency: 3-4 times/week	é	 1.03 (0.82, 1.29) 	92749	24836	92	29.6
Exercise frequency: 5-6 times/week		 0.98 (0.65, 1.48) 	22457	6676	24	28.8
Exercise frequency: Almost everyday]	0.93 (0.71, 1.22)	45038	15135	60	31.7
lead&Neck cancer						
Exercise frequency: None (Reference)	•	1.00 (1.00, 1.00)	403356	148284	377	20.3
Exercise frequency: 1-2 times/week		0.86 (0.71, 1.05)	220601	62923	144	18.2
Exercise frequency: 3-4 times/week	_	0.96 (0.75, 1.24)	92749	24836	73	23.5
Exercise frequency: 5-6 times/week		0.75 (0.44, 1.25)	22457	6676	15	18
Exercise frequency: Almost everyday	· •	 0.96 (0.71, 1.29) 	45038	15135	47	24.9
Cidney cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	301	16.2
Exercise frequency: 1-2 times/week	_ _	 1.10 (0.90, 1.34) 	220601	62923	153	19.3
Exercise frequency: 3-4 times/week		 1.20 (0.93, 1.54) 	92749	24836	75	24.1
Exercise frequency: 5-6 times/week		 0.98 (0.59, 1.62) 	22457	6676	16	19.2
Exercise frequency: Almost everyday	_ +	 1.17 (0.85, 1.60) 	45038	15135	44	23.3
Sallbladder cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	219	11.8
Exercise frequency: 1-2 times/week		0.97 (0.75, 1.25)	220601	62923	83	10.5
Exercise frequency: 3-4 times/week	+	 1.09 (0.79, 1.52) 	92749	24836	43	13.8
Exercise frequency: 5-6 times/week		 1.48 (0.89, 2.45) 	22457	6676	16	19.2
Exercise frequency: Almost everyday	+	 1.32 (0.94, 1.86) 	45038	15135	39	20.6
sophagus cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	214	11.5
Exercise frequency: 1-2 times/week		0.91 (0.70, 1.19)	220601	62923	75	9.5
Exercise frequency: 3-4 times/week		0.76 (0.51, 1.12)	92749	24836	29	9.3
Exercise frequency: 5-6 times/week	· · ·	0.56 (0.25, 1.26)	22457	6676	6	7.2
Exercise frequency: Almost everyday		 0.93 (0.62, 1.37) 	45038	15135	28	14.8

Supplementary Figure 2. Associations of exercise with incident myocardial infarction, stroke, hypertension and Type 2 diabetes (top panel) and various incident cancer outcomes (bottom panel). Note: Cox regression models using age as the underlying timescale were not adjusted for any confounders. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

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Group			HR (95% CI)	Total cases(N)	Unique participants(n) Events(n)	Crud rate
Myocardial infarction							
Exercise frequency: None (Refere	,	†	1.00 (1.00, 1.00)		148033	1526	35.6
Exercise frequency: 1-2 times/wee	∙k —	-	0.89 (0.81, 0.98)	220498	62820	635	27.9
Exercise frequency: 3-4 times/wee		•	0.82 (0.71, 0.94)		24802	246	26
Exercise frequency: 5-6 times/wee		•	0.95 (0.75, 1.20)		6658	74	32.1
Exercise frequency: Almost everyo	lay —	•	0.95 (0.82, 1.11)	45014	15111	197	41.8
Stroke							
Exercise frequency: None (Refere		1	1.00 (1.00, 1.00)		148033	9669	232.
Exercise frequency: 1-2 times/wee			0.86 (0.82, 0.89)		62820	3330	149
Exercise frequency: 3-4 times/wee			0.83 (0.79, 0.88)		24802	1481	160.
Exercise frequency: 5-6 times/wee			0.80 (0.73, 0.89)		6658	389	172.
Exercise frequency: Almost everyo	lay —	•	0.95 (0.90, 1.01)	45014	15111	1239	272.6
Hypertension				400405		05070	
Exercise frequency: None (Refere	,	1	1.00 (1.00, 1.00)		148033	65872	2381
Exercise frequency: 1-2 times/wee			0.92 (0.90, 0.93)		62820	30585	2112
Exercise frequency: 3-4 times/wee			0.86 (0.84, 0.88)		24802	12605	2078
Exercise frequency: 5-6 times/wee		.	0.87 (0.84, 0.90)		6658	3288	2197
Exercise frequency: Almost everyo	lay -	•	0.95 (0.93, 0.97)	45014	15111	7694	2651
Type 2 diabetes							
Exercise frequency: None (Refere	-	1	1.00 (1.00, 1.00)		148033	27101	1456
Exercise frequency: 1-2 times/wee		·	0.92 (0.90, 0.94)		62820	13214	1669
Exercise frequency: 3-4 times/wee			0.87 (0.84, 0.89)		24802	5415	1743
Exercise frequency: 5-6 times/wee			0.88 (0.84, 0.93)		6658	1397	1679
Exercise frequency: Almost everyo	lay	•	0.96 (0.93, 1.00)	45014	15111	3282	1736
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Group		HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Crud rate
Stomach cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	2672	143.0
Exercise frequency: 1-2 times/week	- -	0.90 (0.84, 0.97)	220601	62923	1160	146.6
Exercise frequency: 3-4 times/week		0.87 (0.79, 0.96)	92749	24836	489	157.4
Exercise frequency: 5-6 times/week		0.93 (0.78, 1.10)	22457	6676	139	167
Exercise frequency: Almost everyday	—	0.88 (0.78, 0.98)	45038	15135	328	173.5
Colon cancer						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	1424	76.5
Exercise frequency: 1-2 times/week	_ + •	1.05 (0.95, 1.15)	220601	62923	692	87.4
Exercise frequency: 3-4 times/week	++-	1.06 (0.93, 1.20)	92749	24836	314	101.1
Exercise frequency: 5-6 times/week		1.14 (0.92, 1.41)	22457	6676	90	108.2
Exercise frequency: Almost everyday		0.97 (0.83, 1.12)	45038	15135	191	101
Rectum cancer						
Exercise frequency: None (Reference)	A	1.00 (1.00, 1.00)	403356	148284	809	43.5
Exercise frequency: 1-2 times/week		0.96 (0.85, 1.09)	220601	62923	378	47.8
Exercise frequency: 3-4 times/week		0.88 (0.74, 1.05)	92749	24836	154	49.6
Exercise frequency: 5-6 times/week		1.00 (0.74, 1.35)	22457	6676	46	55.3
Exercise frequency: Almost everyday		0.95 (0.78, 1.16)	45038	15135	107	56.6
ung cancer Exercise frequency: None (Reference)	↓	1.00 (1.00, 1.00)	403356	148284	2138	114.9
Exercise frequency: 1-2 times/week	→ -ĭ	0.90 (0.83, 0.98)	220601	62923	796	100.6
Exercise frequency: 3-4 times/week	→	0.80 (0.71, 0.91)	92749	24836	307	98.8
Exercise frequency: 5-6 times/week	→	0.81 (0.65, 1.01)	22457	6676	85	102.1
Exercise frequency: Almost everyday	· → +	0.93 (0.82, 1.05)	45038	15135	275	145.4
iver cancer						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	1423	76.5
Exercise frequency: 1-2 times/week	++	0.95 (0.87, 1.05)	220601	62923	680	85.9
Exercise frequency: 3-4 times/week	→	0.85 (0.75, 0.98)	92749	24836	263	84.7
Exercise frequency: 5-6 times/week		0.94 (0.74, 1.18)	22457	6676	75	90.1
Exercise frequency: Almost everyday		0.93 (0.79, 1.08)	45038	15135	179	94.7
Pancreas cancer	L I	1 00 (1 00 1 00)	102050	140004	402	20
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	483	26
Exercise frequency: 1-2 times/week		1.02 (0.86, 1.20)	220601	62923	205	25.9
Exercise frequency: 3-4 times/week		1.01 (0.81, 1.27)	92749 22457	24836 6676	92 24	29.6 28.8
Exercise frequency: 5-6 times/week	• '	 0.97 (0.64, 1.46) 0.92 (0.70, 1.20) 	45038	15135	24 60	28.8
Head&Neck cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	377	20.3
Exercise frequency: 1-2 times/week	← Ĭ	0.76 (0.63, 0.93)	220601	62923	144	18.2
Exercise frequency: 3-4 times/week	· • • • • • • • • • • • • • • • • • • •	0.92 (0.71, 1.19)	92749	24836	73	23.5
Exercise frequency: 5-6 times/week		0.73 (0.43, 1.22)	22457	6676	15	18
Exercise frequency: Almost everyday	+	0.92 (0.68, 1.25)	45038	15135	47	24.9
Kidney cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	301	16.2
Exercise frequency: 1-2 times/week		0.95 (0.78, 1.17)	220601	62923	153	19.3
Exercise frequency: 3-4 times/week		1.10 (0.85, 1.42)	92749	24836	75	24.1
Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		 0.93 (0.56, 1.54) 1.11 (0.81, 1.52) 	22457 45038	6676 15135	16 44	19.2 23.3
Sallbladder cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	219	11.8
Exercise frequency: 1-2 times/week		0.98 (0.75, 1.27)	220601	62923	83	10.5
Exercise frequency: 3-4 times/week		1.09 (0.78, 1.52)	92749	24836	43	13.8
Exercise frequency: 5-6 times/week		1.47 (0.88, 2.45)	22457	6676	16	19.2
Exercise frequency: Almost everyday	+	1.30 (0.93, 1.84)	45038	15135	39	20.6
sophagus cancer			100	4 4000 -		4
Exercise frequency: None (Reference)	↑	1.00 (1.00, 1.00)	403356	148284	214	11.5
Exercise frequency: 1-2 times/week		0.86 (0.65, 1.12)	220601	62923	75	9.5
Exercise frequency: 3-4 times/week	·	0.78 (0.52, 1.15)	92749	24836	29	9.3
Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		0.57 (0.25, 1.29) 0.90 (0.60, 1.33)	22457 45038	6676 15135	6 28	7.2 14.8
	- - -	0.30 (0.00, 1.33)	40000	13135	20	14.0
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Supplementary Figure 3. Associations of exercise with incident myocardial infarction, stroke, hypertension and Type 2 diabetes (top panel) and various incident cancer outcomes (bottom panel) after excluding data from the first 2-year follow-up period. Note: Cox regression models using age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of heart disease, stroke or hypertension (in models for incident myocardial infarction, stroke and hypertension), diabetes (in models for incident Type 2 diabetes) or cancer (in models for incident cancer outcomes), smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N"

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indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Abbreviations: HR - Hazard Ratio; CI - Confidence Intervals

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			BMJ C)pen		Body Mass Index ≥25 kg	l 36/bmjopen-20 cted by copyri				
Group	Body Mass Index <25 kg/	Iotal	Unique N) participants((n) Events(i	Crude n) rate	Body Mass Index ≥25 kg)18-025號 ght,確心範	Total cases(N	Unique I) participant	s(n) Events(r	Crude) rate
Myocardial infarction Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week		1.00 (1.00, 1.00) 295683 0.94 (0.84, 1.04) 156729 0.75 (0.63, 0.88) 65633 → 1.16 (0.91, 1.49) 16000		1181 487 163 66	37.5 30 24.4 40.3		See 1	04) 6457	1972	560 236 113 22	49 35.8 40.9 33
Exercise frequency: Almost everyday Stroke Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week	 	0.99 (0.84, 1.17) 31821 1.00 (1.00, 1.00) 295683 0.85 (0.81, 0.89) 156729	44670	150 6877 2227	45 225.1 139.9		irch 2019Dov hSeignement es relatedet of	.11) 13217 .00) 107673 .96) 63872	4477 39529 18253	69 2812 1106	49.8 254.4 171.8
Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday Hypertension		0.82 (0.77, 0.88) 65633 0.82 (0.73, 0.93) 16000 0.94 (0.87, 1.01) 31821	17543 4704 10658	990 272 842	151.2 169.6 262.2		© 0 0 1 © Wineoaded 1 © © Wineoaded 1 © © Wineoaded 1 © © Wineoaded 1 © © Wineoaded 1	94) 6457	1972	492 118 398	182 181.7 298.1
Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	+ + +	1.00 (1.00, 1.00) 295683 0.92 (0.91, 0.94) 156729 0.85 (0.83, 0.87) 65633 0.86 (0.82, 0.90) 16000 0.95 (0.92, 0.98) 31821		44055 19638 7967 2079 4984	2061 1796.3 1745 1838.9 2296.9		i to o t i to no		39529 18253 7293 1972 4477	21909 10985 4650 1215 2721	3474.6 3093.3 3098.2 3310.1 3709.4
Type 2 diabetes Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	+ + +	1.00 (1.00, 1.00) 295683 0.93 (0.90, 0.95) 156729 0.88 (0.85, 0.92) 65633 0.88 (0.82, 0.95) 16000 0.99 (0.95, 1.04) 31821		17229 7975 3291 844 2044	613.2 552.4 548.3 575.7 697.4	+ + +	A10 (1.89, 1 P2 (0.89, 0 P2 (.00) 107673 .95) 63872 .91) 27116	39529 18253 7293 1972 4477	9899 5251 2130 555 1241	1031.5 947.9 910.9 986.6 1069.5
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Group		Smoking: ne	VET Total Unique HR (95% CI) cases(N) participants(n) Eve	Crude ents(n) rate	Smoking: prev	Total Unique	Crude ants(n) Events(n) rate	018-018-018-018-018-018-018-018-018-018-	Ent Total Unique HR (95% CI) cases(N) participa	
Exercise fre Exercise fre Exercise fre	infarction requency: None (Reference) requency: 1-2 times/week requency: 3-4 times/week requency: 5-6 times/week requency: Almost everyday		1.00 (1.00, 1.00) 296225 106647 101 0.86 (0.76, 0.96) 130907 37173 333 0.73 (0.61, 0.86) 60735 16199 133 0.74 (0.53, 1.03) 15420 4593 37 0.99 (0.83, 1.18) 32360 10849 139	24.8 22.3 23.5		1.00 (1.00, 1.00) 23702 8659 0.64 (0.48, 0.86) 28268 7571 0.72 (0.50, 1.03) 12863 3156 → 1.17 (0.71, 1.92) 3027 831 0.78 (0.49, 1.24) 4496 1337	132 52.1 75 25.7 40 30.5 18 58.2 21 44.5	590 on 13 Iuding for	1.00 (1.00, 1.00) 83399 32978 0.94 (0.81, 1.08) 61426 18179 0.89 (0.72, 1.10) 19151 5481 1.28 (0.90, 1.82) 4010 1252 0.87 (0.67, 1.14) 8162 2949	598 315 99 33 59
Exercise fro Exercise fro Exercise fro	requency: None (Reference) requency: 1-2 times/week requency: 3-4 times/week requency: 5-6 times/week requency: Almost everyday		1.00 (1.00, 1.00) 298225 108647 717 0.87 (0.83, 0.91) 130907 37173 217 0.84 (0.79, 0.90) 60735 16199 105 0.76 (0.60, 0.86) 15420 4593 271 0.95 (0.88, 1.01) 32380 10849 909	1 165.6 0 175.3 176.5		1.00 (1.00, 1.00) 23702 8659 0.91 (0.79, 1.05) 28268 7571 0.77 (0.64, 0.93) 12863 3156 0.97 (0.74, 1.28) 3027 831 1.05 (0.85, 1.29) 4496 1337	507 205.3 363 126.4 148 114.8 56 184.8 112 245.4	March uses r ↓↓↓	1.00 (1.00, 1.00) 83399 32978 0.82 (0.75, 0.89) 61426 18179 0.85 (0.75, 0.96) 19151 5481 0.79 (0.61, 1.01) 4010 1252 0.92 (0.80, 1.06) 8162 2949	2008 799 284 63 219
Exercise fre Exercise fre Exercise fre	n requency: None (Reference) requency: 1-2 times/week requency: 3-4 times/week requency: 5-6 times/week requency: Almost everyday	+ + +	1.00 (1.00, 1.00) 298225 106847 479 0.88 (0.88, 0.91) 130907 37173 179 0.82 (0.81, 0.84) 60735 16199 806 0.86 (0.82, 0.89) 15420 4693 222 0.93 (0.90, 0.95) 32380 10849 555	68 2035.9 6 1979.9 3 2110.5	+ + +	1.00 (1.00, 1.00) 23702 8659 0.91 (0.87, 0.95) 28268 7571 0.88 (0.83, 0.93) 12863 3156 0.97 (0.79, 0.96) 3027 831 0.96 (0.88, 1.04) 4496 1337	4168 2733.5 3967 2282.3 1791 2339.4 446 2396.9 708 2629.5	019. Do nemen ated to	1.00 (1.00, 1.00) 83399 32978 0.98 (0.95, 1.01) 61426 18179 0.97 (0.93, 1.01) 19151 5481 0.95 (0.88, 1.03) 4010 1252 1.03 (0.97, 1.09) 8162 2949	1387 8688 2740 625 1441
Exercise fr Exercise fr Exercise fr	etes requency: None (Reference) requency: 1-2 times/week requency: 3-4 times/week requency: 5-6 times/week requency: Almost everyday	+ + +	1.00 (1.00, 1.00) 296225 106647 188 0.90 (0.88, 0.93) 130907 37173 733 0.86 (0.83, 0.89) 60735 16199 337 0.87 (0.81, 0.93) 15420 4593 868 0.97 (0.93, 1.01) 32380 10849 231	6 612.3 614.8 633.9		1.00 (1.00, 1.00) 23702 8659 0.90 (0.84, 0.97) 28268 7571 0.90 (0.83, 0.98) 12863 3156 0.87 (0.75, 1.01) 3027 831 0.98 (0.87, 1.11) 4496 1337	1691 776.7 1685 669.5 787 693.5 196 733 322 793	ownloaded fro ttSuperieur (A text and data	1.00 (1.00, 1.00) 83399 32978 0.95 (0.91, 0.98) 61426 18179 0.87 (0.82, 0.93) 1915 5481 0.96 (0.85, 1.07) 4010 1252 0.95 (0.88, 1.03) 8162 2949	6579 4205 1257 314 650
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Group	Alcohol consumption	Total	Unique		Crude	Alcohol consumption	n: 2-3times/month	Unique participants(20514	cted by copyright, in
		HR (95% CI) cases(N	 participan 	s(n) Events(n) rate		HR (95% CI) cases(N	participants(n) Event ())
vocardial infarction exercise frequency: None (Reference)		1.00 (1.00, 1.00) 263051	95580	1164	41.9		1.00 (1.00, 1.00) 54349	20514	186 Idin
xercise frequency: 1-2 times/week	_	0.89 (0.79, 1.00) 101852	29973	364	34.8	+	0.92 (0.74, 1.15) 48252	13400	147 (0
xercise frequency: 3-4 times/week		0.80 (0.68, 0.95) 45914	12548	150	32.4	•	→ 0.97 (0.72, 1.31) 18554	4897	57 11 Č
xercise frequency: 5-6 times/week xercise frequency: Almost everyday	· _	0.95 (0.71, 1.27) 11619 0.90 (0.76, 1.08) 26299	3489 8971	47 134	39.8 48.9		 0.74 (0.40, 1.36) 4353 0.74 (0.46, 1.19) 6456 	1255 2127	¹¹ 19
oke									JSC 1
xercise frequency: None (Reference)	+	1.00 (1.00, 1.00) 263051		6896	256.7	+	1.00 (1.00, 1.00) 54349	20514	886 BS
xercise frequency: 1-2 times/week xercise frequency: 3-4 times/week		0.88 (0.83, 0.92) 101852 0.84 (0.78, 0.90) 45914	29973 12548	1890 880	185 194.9		0.81 (0.73, 0.91) 48252 0.76 (0.65, 0.89) 18554	13400 4897	⁵³⁶ 202
xercise frequency: 5-6 times/week		0.78 (0.69, 0.90) 11619	3489	227	194.9		0.80 (0.61, 1.04) 4353	1255	202 P 57 D
xercise frequency: Almost everyday	-+-	0.96 (0.89, 1.03) 26299	8971	821	312.7		- 0.98 (0.82, 1.18) 6456	2127	57 130 lated
pertension			0.000-0		0000			005	-
xercise frequency: None (Reference) xercise frequency: 1-2 times/week	_ †	1.00 (1.00, 1.00) 263051 0.90 (0.88, 0.92) 101852		42572 13905	2321.6 1961.7	†	1.00 (1.00, 1.00) 54349 0.92 (0.89, 0.96) 48252	20514 13400	
xercise frequency: 1-2 times/week xercise frequency: 3-4 times/week	+	0.84 (0.81, 0.86) 45914	12548	6155	1954.5	→	0.84 (0.80, 0.88) 18554	4897	6205 2253 t
xercise frequency: 5-6 times/week	→	0.84 (0.80, 0.88) 11619	3489	1644	2031.8	→ –	0.91 (0.84, 0.99) 4353	1255	595 🔒
xercise frequency: Almost everyday	+	0.93 (0.90, 0.96) 26299	8971	4507	2575.7	_	1.01 (0.95, 1.08) 6456	2127	⁶²⁰⁵ ²²⁵³ ⁵⁹⁵ ¹⁰⁰⁶ and
e 2 diabetes xercise frequency: None (Reference)		1.00 (1.00, 1.00) 263051	95580	17226	698.4		1.00 (1.00, 1.00) 54349	20514	
kercise frequency: 1-2 times/week	+	0.92 (0.89, 0.95) 101852		5933	636.5	—	0.93 (0.88, 0.98) 48252	13400	2649 D
xercise frequency: 3-4 times/week	+	0.88 (0.84, 0.91) 45914	12548	2656	641.7	→	0.85 (0.79, 0.91) 18554	4897	954 0
xercise frequency: 5-6 times/week xercise frequency: Almost everyday		0.93 (0.87, 1.01) 11619 0.98 (0.94, 1.03) 26299	3489 8971	743 1949	706.6 813.9		0.82 (0.72, 0.94) 4353 0.97 (0.87, 1.08) 6456	1255 2127	²²⁹ 397 minin
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A	Icohol consumption:	1-2times/week							
		Total	Unique	e(n) Evente	Crude	Alcohol consumption	Total	Unique	trair
Sroup		Total	Unique I) participan	s(n) Events(Alcohol consumption	Total	Unique participants(i	n) Evente(n)
iroup ocardial infarction		Total		s(n) Events(Alcohol consumption	Total	Unique participants(13783	n) Eventarin ng
ocardial infarction xercise frequency: None (Reference) xercise frequency: 1-2 times/week		Total HR (95% CI) Cases(N 1.00 (1.00, 1.00) 51117 0.87 (0.70, 1.08) 51538	 N) participan 18407 13815 	197 152	n) rate 36 28.5	Alcohol consumption	Total HR (95% CI) cases(N) 1.00 (1.00, 1.00) 34839 0.70 (0.52, 0.95) 18959	participants(13783 5735	n) Eventarin ng
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roup ocardial infarction xercise frequency: None (Reference) xercise frequency: 1-2 times/week xercise frequency: 5-6 times/week		Total HR (95% CI) Cases(N 1.00 (1.00, 1.00) 51117 0.87 (0.70, 1.08) 51538	 N) participan 18407 13815 	197 152	n) rate 36 28.5		Total HR (95% CI) cases(N) 1.00 (1.00, 1.00) 34839 0.70 (0.52, 0.95) 18959	participants(13783 5735	¹⁹⁴ ⁶⁰ ²⁴ ¹⁹ ³³
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roup cardial infarction xercise frequency: None (Reference) xercise frequency: 3-4 times/week xercise frequency: 3-4 times/week xercise frequency: 3-4 times/week xercise frequency: None (Reference) xercise frequency: 1-2 times/week xercise frequency: 3-4 times/week xercise frequency: 3-4 times/week xercise frequency: 1-0 times/week xercise frequency: 1-2 times/week xercise frequency: 1-2 times/week xercise frequency: 3-4 times/week xercise frequency: 3-6 times/week xercise frequency: 5-6 times/week xercise frequency: None (Reference) xercise frequency: 1-2 times/week xercise frequency: 1-2 times/week		Total HR (95% Cl) cases(N 1.00 (1.00, 1.00) 51117 0.87 (0.70, 1.08) 51538 0.68 (0.49, 0.44) 19850 0.78 (0.42, 1.43) 4161 1.07 (0.74, 1.55) 7213 1.00 (1.00, 1.00) 51117 0.83 (0.74, 0.92) 51538 0.87 (1.74, 1.14) 4161 0.86 (0.72, 1.04) 7213 1.00 (1.00, 1.00) 51117 0.91 (0.84, 0.94) 51538 0.91 (0.84, 0.94) 51538 0.91 (0.84, 0.94) 51538 0.91 (0.84, 0.99) 4161 0.96 (0.91, 1.03) 7213 1.00 (1.00, 1.00) 51117 1.00 (1.00, 1.00) 51137 0.96 (0.91, 1.03) 7213 1.00 (1.00, 1.00) 51138 0.86 (0.86, 0.95) 51538 0.86 (0.86, 0.95) 51538 0.86 (0.80, 0.92) 218850	 articipan articipan 18407 13815 5027 1209 2200 	197 152 45 11 33 902 574 246 58 132 8339 7151 2782 609 1174 3526 3185 1181	n) rate 36 28.5 22 25.4 43.6 168.3 109.2 122.4 136.7 179 2487.2 2291.1 231.8 2331.8 2331.8 2691.4 748.6 693 664.8	Alcohol consumption	Total Total HR (95% CI) cases(N) 1.00 (1.00, 1.00) 34839 0.70 (0.52, 0.55) 19859 0.64 (0.42, 0.88) 8431 1.67 (1.04, 2.68) 2324 1.15 (0.79, 1.66) 5070 1.00 (1.00, 1.00) 34839 0.88 (0.77, 1.00) 19959 0.88 (0.77, 1.00) 19959 0.89 (0.77, 1.00) 19959 0.88 (0.77, 1.00) 19959 0.89 (0.60, 1.07) 2324 0.94 (0.79, 1.11) 5070 1.00 (1.00, 1.00) 34839 0.98 (0.84, 1.02) 18959 0.92 (0.87, 0.37) 8431 0.99 (0.92, 1.05) 5070 1.00 (1.00, 1.00) 34839 0.88 (0.78, 0.35) 18959 0.89 (0.84, 0.55) 18559 0.88 (0.78, 0.53) 18559 0.89 (0.84, 0.55) 18559 0.88 (0.78, 0.53) 18559 0.89 (0.84, 0.55) 18559 0.88 (0.78, 0.53) 18559	participants() 13783 5735 2364 723 1837 13783 5735 2364 723 1837 13783 5735 2364 723 1837 13783 5735 2364 13783 5735 2364	n) Eventally 194 194 194 195 24 195 233 154 157 154 157 154 157 154 157 154 157 157 157 157 157 157 157 157
ocardial infarction xercise frequency: None (Reference)		Total HR (95% Cl) cases(N 1.00 (1.00, 1.00) 51117 0.87 (0.70, 1.08) 51538 0.68 (0.49, 0.94) 19850 0.78 (0.42, 1.43) 4161 1.00 (1.00, 1.00) 51117 0.83 (0.74, 0.92) 51538 0.88 (0.67, 1.14) 19850 0.87 (0.74, 1.55) 7213 1.00 (1.00, 1.00) 51117 0.88 (0.67, 1.14) 4161 0.88 (0.67, 1.14) 4161 0.86 (0.72, 1.04) 7213 1.00 (1.00, 1.00) 51117 0.91 (0.84, 0.99) 4161 0.96 (0.91, 1.03) 7213 1.00 (1.00, 1.00) 51117 0.90 (0.86, 0.95) 51538 0.86 (0.80, 0.92) 19850 0.91 (0.86, 0.95) 51538 0.86 (0.80, 0.92) 19850 0.83 (0.73, 0.94) 4161 0.96 (0.80, 0.92) 19850	 Participan 18407 13815 5027 1209 2200 18407 13815 5027 1209 1209 18407 13815 5027 1209 1209 	197 152 45 11 33 902 574 246 58 132 8339 7151 2782 609 1174 3526 3185 1181 244	n) rate 36 28.5 22 25.4 43.6 168.3 109.2 122.4 138.7 179 2487.2 2291.1 2313.3 2331.8 2691.4 748.6 693 664.8 647.3	Alcohol consumption	Total Total HR (95% CI) cases(N) 1.00 (1.00, 1.00) 34839 0.70 (0.52, 0.35) 19859 0.64 (0.42, 0.38) 8431 → 1.67 (1.04, 2.68) 2324 → 1.15 (0.79, 1.86) 5070 1.00 (1.00, 1.00) 34839 0.88 (0.77, 1.00) 18959 0.83 (0.70, 0.38) 8431 0.80 (0.60, 1.07) 2324 0.94 (0.79, 1.11) 5070 1.00 (1.00, 1.00) 34839 0.92 (0.87, 0.97) 8431 0.93 (0.85, 1.03) 2324 0.93 (0.85, 1.03) 2324 0.99 (0.92, 1.05) 5070 1.00 (1.00, 1.00) 34839 0.88 (0.78, 0.33) 8331 0.89 (0.84, 0.55) 18559 0.85 (0.78, 0.33) 831 0.86 (0.73, 0.99) 2324	participants() 13783 5735 2364 723 1837 13783 5735 2364 723 1837 13783 5735 2364 723 1837 13783 5735 2364 723 1837	n) Eventary 194 194 194 195 24 195 233 154 157 156 235 154 157 156 235 235 154 157 154 157 154 157 156 157 157 157 157 157 157 157 157

Myocardial Infaction Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: Almost everyday Stoke Exercise frequency: Almost everyday Stoke Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4	Ecipants(n) Events(n) rate 2298 1576 41.2 170 621 31.7 984 237 29.9 73 76 40.7 195 46.8 195 46.8 195 236 170 2817 146.4 944 1212 156.1 73 328 174.9 481 1109 275.9 2298 58611 2366.4 170 25975 2066.5 944 10332 2005.9 73 2710 2149.4 481 6797 2627	intervention of the second sec	1.00, 1.00) 439 0.66, 1.09) 313 0.49, 0.39) 1511 0.35, 127) 382 0.65, 1.54) 530 1.00, 1.00) 439 0.77, 1.02) 1511 0.59, 0.99) 382 0.76, 1.10) 530 1.00, 1.00) 439 1.00, 1.00) 439 0.88, 0.99) 312 0.88, 0.99) 312 0.88, 0.99 382 0.94, 1.06) 530	s(N) participants(n) 14 15986 13 8753 15 3942 101 3 15 103 15 3942 103 8753 155 3942 103 8753 155 3942 103 1654 14 15986 155 3942 15 1654 14 15986 155 3942 1654 103 155 3942 155 3942 155 3942 103 103	165 102 39 10 24 933 516 62 131 7353 4648 2285 58 808
Exercise frequency: None (Reference) Exercise frequency: 3-4 times/week Exercise frequency: 1-2 times/week Exercise frequency: 5-6 time	170 621 31.7 184 237 29.9 73 78 40.7 181 195 46.8 12298 6756 236 170 2817 146.4 184 1212 156.1 173 328 174.9 181 1109 275.9 2298 58611 2366.4 170 25975 2066.5 384 10332 2005.9 73 2710 2149.4 181 6797 2627 Unique Cn participants(n) Events(n) rat 261	A BA 0.84 0.70 0.67 0.87 0.89 0.76 0.91 0.91 0.91 0.91 0.91 0.93 0.92 0.93 0.92 0.93	0.66, 1.09 313 0.49, 0.99 151 0.35, 1.27 382 0.65, 1.54 530 1.00, 1.00 438 0.78, 0.97 313 0.77, 1.02 151 0.59, 0.98 382 0.78, 1.10 530 1.00, 1.00 439 3.02, 78, 1.10 530 1.00, 1.00 439 3.088, 0.97 151 0.88, 0.99 382 0.88, 0.97 151 0.88, 0.99 382 0.84, 1.08 530	33 8753 35 3942 30 103 30 1054 44 15986 33 8753 35 3942 36 103 37 103 38 1654 44 15986 33 8753 34 15986 35 3942 36 103 375 3942 36 1103 375 3942 36 1654	102 39 10 24 933 516 52 131 7353 4648 2285 584 908
Exercise frequency: 1-2 times/week 0.87 (0.78, 0.89) 186236 54170 Exercise frequency: 3-4 times/week 0.87 (0.78, 0.89) 186236 54170 Exercise frequency: 3-4 times/week 0.81 (0.70, 0.89) 7754 2084 Exercise frequency: Almost everyday 0.83 (0.80, 1.09) 39732 13461 Stroke 0.83 (0.80, 1.09) 39732 13461 Exercise frequency: None (Reference) 0.86 (0.82, 0.90) 180236 54170 Exercise frequency: Almost everyday 0.86 (0.82, 0.90) 180236 54170 Exercise frequency: Almost everyday 0.86 (0.82, 0.90) 180236 54170 Exercise frequency: Almost everyday 0.86 (0.82, 0.90) 180236 54170 Exercise frequency: Almost everyday 0.86 (0.80, 0.87) 7754 2084 Exercise frequency: Almost everyday 0.86 (0.83, 0.87) 7754 2084 Exercise frequency: Almost everyday 0.87 (0.84, 0.80) 18631 5573 Exercise frequency: Almost everyday 10.37 (0.40, 0.90) 18631 5573 Exercise frequency: Almost everyday 10.37 (0.40, 0.90) 18631 5573 Exercise frequenc	170 621 31.7 184 237 29.9 73 78 40.7 181 195 46.8 12298 6756 236 170 2817 146.4 184 1212 156.1 173 328 174.9 181 1109 275.9 2298 58611 2366.4 170 25975 2066.5 384 10332 2005.9 73 2710 2149.4 181 6797 2627 Unique Cn participants(n) Events(n) rat 261	A BA 0.84 0.70 0.67 0.87 0.89 0.76 0.91 0.91 0.91 0.91 0.91 0.93 0.92 0.93 0.92 0.93	0.66, 1.09 313 0.49, 0.99 151 0.35, 1.27 382 0.65, 1.54 530 1.00, 1.00 438 0.78, 0.97 313 0.77, 1.02 151 0.59, 0.98 382 0.78, 1.10 530 1.00, 1.00 439 3.02, 78, 1.10 530 1.00, 1.00 439 3.088, 0.97 151 0.88, 0.99 382 0.88, 0.97 151 0.88, 0.99 382 0.84, 1.08 530	33 8753 35 3942 30 103 30 1054 44 15986 33 8753 35 3942 36 103 37 103 38 1654 44 15986 33 8753 34 15986 35 3942 36 103 375 3942 36 1103 375 3942 36 1654	102 39 10 24 933 516 52 131 7353 4648 2285 584 908
Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: 4-4 times/week Exercise frequency: Almost everyday Broke Exercise frequency: 4-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: 4-4 times/week Exercise frequency: 1-2 times/week Exercise frequency: 4-4 times/week Exercise frequency: 1-2 times/week Exercise frequency: 5-6 ti	384 237 29.9 73 76 40.7 181 195 46.8 2298 8756 236 170 2817 146.4 394 1212 156.1 173 328 174.9 181 1109 275.9 2298 58611 2864.5 170 25875 2066.5 394 10332 2005.9 73 2710 2149.4 181 6797 2627 Unique Cn participants(n) Events(n) rat	A C C C C C C C C C C C C C C C C C C C	0.49,0.99 1511 0.35,1.27) 3820 0.65,1.54) 530 1100,1.00) 439 0.76,1.00 439 0.77,1.02 1511 0.59,0.89 382 0.76,1.10 530 1100,1.00 439 0.88,0.97 1511 0.88,0.99 382 0.88,0.97 1511	55 3942 6 1103 7 1654 14 15986 13 8753 15 3942 6 1103 75 3942 6 1103 7 1654 14 15986 15 3942 1654 155 15 3942 15 3942 1103 8753 15 3942 1103 1654	39 10 24 933 516 270 62 131 7353 4648 2285 584 908
Exercise frequency: 5-8 times/week 1.04 (0.83, 1.31) 18631 5573 Exercise frequency: Almost everyday 0.83 (0.80, 1.09) 39732 13461 Stroke 1.00 (1.00, 1.00) 359412 13224 Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 359412 13224 Exercise frequency: 3-4 times/week 0.82 (0.87, 0.89) 108298 64174 Exercise frequency: Almost everyday 0.82 (0.87, 0.89) 108298 64174 Exercise frequency: Almost everyday 0.82 (0.87, 0.89) 108298 64174 Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 359412 13224 Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 359412 13224 Exercise frequency: Almost everyday + 0.85 (0.80, 0.87) 71584 2084 Exercise frequency: Almost everyday + 0.87 (0.84, 0.90) 16831 5573 Exercise frequency: Almost everyday + 0.87 (0.84, 0.90) 16831 5573 Exercise frequency: Almost everyday + 0.87 (0.84, 0.80) 1681 5573 Type 2 diabetes Exercise frequency: 1.2 times/week +	73 78 40.7 181 195 46.8 2298 8756 236 170 2817 146.4 184 1212 156.1 73 328 174.9 181 1109 275.9 2298 58611 2366.4 170 25975 2066.5 170 2149.4 181 6797 2627 Unique Cri participants(n) Events(n) rat	Gamma Control of the second se	0.35, 127) 382 0.65, 1.54) 530 1.00, 1.00) 439 0.78, 0.97) 313 0.77, 100 1.00, 1.00) 439 0.77, 100 1.00, 1.00) 530 0.76, 1.10) 530 0.88, 0.96) 313 0.88, 0.97) 151 0.83, 0.99 382 0.94, 1.08) 530	3 1103 3 1654 14 15986 13 8753 15 3942 5 1103 3 1654 14 15986 13 8753 14 15986 13 8753 15 3942 15 3942 15 3942 15 3942 15 1103 15 1654	10 24 933 516 270 62 131 7353 4648 2285 584 908
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Exercise frequency: None (Reference) Exercise frequency: -2 times/week Exercise fre	170 25975 2066.5 984 10332 2005.9 73 2710 2149.4 181 6797 2627 Unique Cn participants(n) Events(n) rat	Family history of diabetes	0.89, 0.96) 313 0.88, 0.97) 151 0.83, 0.99) 382 0.94, 1.08) 530	33 8753 35 3942 5 1103 5 1654	4648 2285 584 908
Exercise frequency: 1-2 times/week Exercise frequency: -3 times/week Exercise frequency: -3 times/week Exercise frequency: Almost everyday	170 25975 2066.5 984 10332 2005.9 73 2710 2149.4 181 6797 2627 Unique Cn participants(n) Events(n) rat	Family history of diabetes	0.89, 0.96) 313 0.88, 0.97) 151 0.83, 0.99) 382 0.94, 1.08) 530	33 8753 35 3942 5 1103 5 1654	4648 2285 584 908
Exercise frequency: 3-4 times/week 0.85 (0.83, 0.87) 7754 2084 0.87 (0.84, 0.90) 1683 5573 0.94 (0.92, 0.97) 39732 13 1 1 3 1 1.3 Total Or the service frequency: Almost everyday Total 1 1.3 Total U Group Total U Total U Total U Group HR (95% Cl) cases(N) properties Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 382331 1 Exercise frequency: 1-2 times/week 0.91 (0.89, 0.94) 205395 5229 22 Exercise frequency: 5-6 times/week 0.88 (0.83, 0.93) 20452 60 	894 10332 2005.9 73 2710 2149.4 181 6797 2627 Unique Cr participants(n) Events(n) rat	Family history of diabetes	0.88, 0.97) 1511 0.83, 0.99) 382 0.94, 1.08) 530	35 3942 5 1103 6 1654	2285 584 908
Exercise frequency: 5-6 times/week	73 2710 2149.4 181 6797 2627 Unique Cr participants(n) Events(n) rat	Family history of diabetes	0.83, 0.99) 3820 0.94, 1.08) 5300	5 1103 5 1654	584 908
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Group HR (95% Cl) cases(N) pr Type 2 diabetes	participants(n) Events(n) rat		5% CI) case	s(N) participants((n) Ever
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Exercise frequency: 5-6 times/week 0.88 (0.83, 0.93) 20452 60	30410 11828 03	0.80 (5.08, 1.03) 1320	4010	1207
	22716 4818 62	25.2 0.89 (0.81, 0.98) 7520	2120	603
Exercise frequency: Almost everyday 0.97 (0.93, 1.00) 42346 1	6064 1234 66	64.1 0.91 (0.78, 1.07) 2005	612	165
Line one in equency. Allitest everyday 0.87 (0.83, 1.00) 42340 14	14280 3050 78	89.1 0.95 (0.83, 1.09) 2692	855	235
	14200 5050 70	0.33 (203, 1.03) 203	. 655	200
.3 1 1.3		1 1.3			

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Group	Men	HR (95% CI)	Total	Unique) participants(n) Evente/a	Crude	Women		Total	Unique	s(n) Events(i	Cru
Gloup		HK (95% CI)	Cases(IN)) participants(n) Events(n) Tale			Cases(IN) participants		11)140
yocardial infarction												
Exercise frequency: None (Reference)	†	1.00 (1.00, 1.00)	190188	64984	1134	56.1	†			83300	607	26
Exercise frequency: 1-2 times/week	— –	0.85 (0.77, 0.95)		39851	571	37.4		022 (0.7▲1.10) 0288 5 29, 0.89) → 0292 60, 1.41)	73310	23072	152	20
Exercise frequency: 3-4 times/week	_	0.83 (0.72, 0.96)		14273	219	37.5		0,89) 0.89	35787	10563	57	15
Exercise frequency: 5-6 times/week	•	→ 1.01 (0.79, 1.30)		3532	66	50.6		\rightarrow 0.092 $\overline{00}$.60, 1.41)	9823	3144	22	22
Exercise frequency: Almost everyday		0.97 (0.82, 1.14)	24084	7509	156	61.8		- (13200172, 1.21) (120172, 1.21) (120190172, 1.21) (120190172, 1.21) (120190172, 1.21) (120190172, 1.21)	20954	7626	63	28
troke								019 ate				
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	190188	64984	4312	219.3	+	100.7.1.00, 1.00)	213168	83300	5377	24
Exercise frequency: 1-2 times/week	→	0.84 (0.79, 0.89)	147291	39851	1953	130	→	0,99 🕰 .8 🖉 0.94)	73310	23072	1380	18
Exercise frequency: 3-4 times/week	→	0.84 (0.78, 0.91)		14273	824	143.8	→	0.82 (0.78, 0.89)	35787	10563	658	18
Exercise frequency: 5-6 times/week	→	0.81 (0.70, 0.93)	12634	3532	209	163.5	-	0 0 9 00 .65, 0.92)	9823	3144	181	18
Exercise frequency: Almost everyday	-+	0.95 (0.88, 1.04)	24084	7509	658	270.3	-+	1990,800,899 0924,800,899 0924,800,899 0924,800,899 0924,800,899 0924,800,899 0924,800,899 0924,800,899 0924,800,899 0924,800,899 0924,800,899 0924,800,899 0924,800,899 0924,800,899 0924,800,809 000,800,800,800 000,800,800,800,800,800	20954	7626	582	27
ypertension								nd 2011				
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	190188	64984	30839	2512.4	+	<u>, o (1.00</u> , 1.00)	213100	83300	35125	22
Exercise frequency: 1-2 times/week	•	0.94 (0.93, 0.96)	147291	39851	20448	2241.5	+	0 .87 (0.8 2 , 0.89)	73310	23072	10175	18
Exercise frequency: 3-4 times/week	+	0.92 (0.90, 0.94)	56962	14273	7874	2278.6	+	(TO 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	05707	10563	4743	18
Exercise frequency: 5-6 times/week	- - -	0.93 (0.88, 0.97)	12634	3532	1911	2465.2	→	0,32,0.87)	9823	3144	1383	19
Exercise frequency: Almost everyday	+	1.00 (0.97, 1.03)	24084	7509	4126	2856.7	→	(1994) (1992) (1	20954	7626	3579	24
rpe 2 diabetes								<u> </u>				
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	190188	64984	14006	813.4	+	1.00 (1.03, 1.00)	213168	83300	13122	64
Exercise frequency: 1-2 times/week	+	0.91 (0.89, 0.94)	147291	39851	9229	703.8	→	1 00 (1.00 1.00) 0.91 (0.88 0.95)	73310	23072	3997	58
Exercise frequency: 3-4 times/week	→	0.87 (0.84, 0.90)	56962	14273	3486	692.3	→		35787	10563	1935	58
Exercise frequency: 5-6 times/week	_ •_	0.88 (0.82, 0.94)	12634	3532	834	746.7	_		9823	3144	565	6
Exercise frequency: Almost everyday	- - -	0.93 (0.88, 0.98)	24084	7509	1764	823.2	- +	1 3 (0. 3 1.08)	20954	7626	1521	78

Supplementary Figure 4. Results from running Cox regression models examining effect modification of sex, zody mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequence and incident myocardial infarction, stroke, hypertension and type 2 diabetes. Note: Cox regression models using age as the underlying timescale were adjusted for sex [not in models for effect modification by sex], body mass index [not in models for effect modification by body mass index], systolic blood pressure, fasting glucose levels, total cholesterol levels, family history [not in models for effect modification by family history of respective disease] of heart disease/stroke/hypertension (in models for myocardial infarction, stroke and hypertension), or diabetes (in models for effect modification by alcohol consumption]. Or ude rates are perfect modification by smoking status] and alcohol consumption [not in models for effect modification by alcohol consumption]. Crude rates are perfect 00,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. P-values for multiplicative terms – myocardial pfarction (p-value = 0.235), stroke (p-value = 0.363), hypertension (p-value = 0.050) and type 2 diabetes (p-value = 0.196) by body mass index;

Page 45 of 50	BMJ Open BMJ Open BMJ Open
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42	BMI Open myocardial infarction (p-value = 0.643), stroke (p-value = 0.661), hypertension (p-value = 0.001) and type 2 diabetes (p-value = 0.980) by smoking; myocardial infarction (p-value = 0.300), stroke (p-value = 0.500), stroke (p-value = 0.250),
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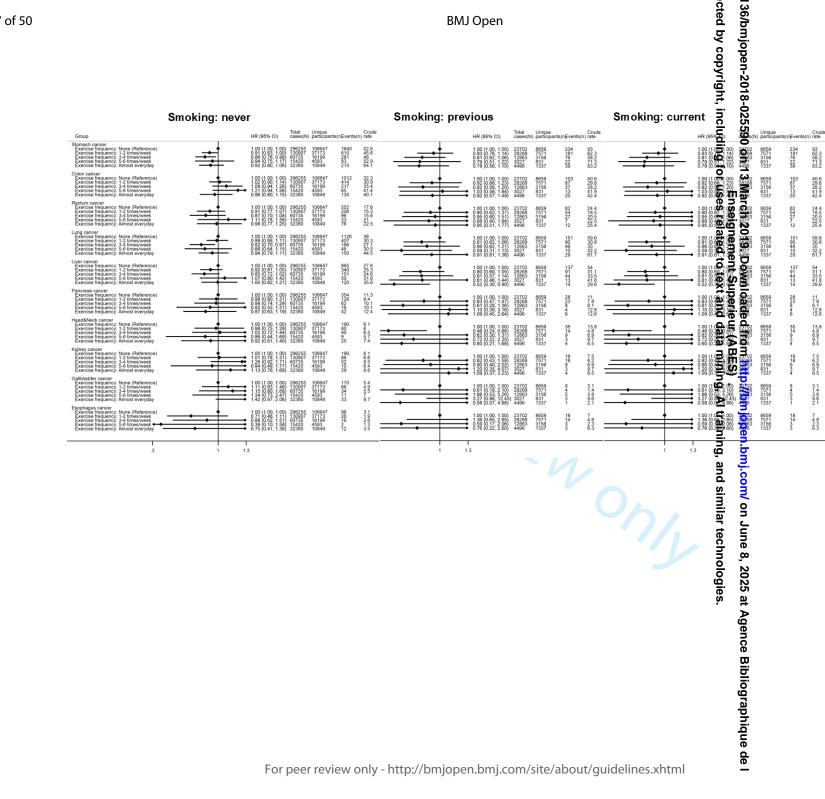
l36/bmjopen-2018-025590 on 13 March 2019. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l sted by copyright, including for uses related to text and data mining, Artaining, and similar technologies.

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Ableck-cancer 1.00 (1.00, 1.00) 295683 108755 288 9.1 1.00 (1.00, 1.00) Incise frequency: None (Reference) 0.75 (0.59, 0.94) 156729 44670 101 6.2 0.80 (0.55) Incise frequency: 5-4 limes/week 0.83 (0.61, 1.14) 65633 17543 47 7 0.80 (0.57) Incise frequency: 5-6 limes/week 0.34 (0.27, 1.09) 10000 1002 11.20 (12, 1.12) 11.20 (12, 1.12) 11.20 (12, 1.12) 11.20 (12, 1.12) 11.20 (12, 1.12) 11.20 (12, 1.12) 11.20 (12, 1.12) 11.20 (12, 1.12) 0.84 (0.67, 1.34) 31.62 1 0.80 (0.85) 0.81 (0.8) 0.84 (0.8) </td <td>1.16) 63872 1.75) 27116 2.62) 6457</td> <td>39529 18253 7293 1972 4477</td> <td>89 43 26 7 11</td>	1.16) 63872 1.75) 27116 2.62) 6457	39529 18253 7293 1972 4477	89 43 26 7 11
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Jagus zancer 1.00 (1.00, 1.00) 295683 108755 188 5.9 ricise frequency: 1-2 times/week 0.89 (0.66, 1.18) 156729 44670 66 4.1 1.00 (1.00, 1.00) ricise frequency: 5-4 times/week 0.69 (0.66, 1.18) 156729 44670 66 4.1 1.00 (1.00, 1.00) ricise frequency: 5-4 times/week 0.65 (0.29, 1.48) 16000 1704 6 3.6 310 (0.60, 1.35 (0.52, 1.23) 1352 (1.123) 1352 (1.123) 1352 (1.123) 1352 (1.123) 1352 (1.123) 1352 (1.123) 135 (1.123)<	1.00) 107673 1.25) 63872 2.81) 27116	39529 18253 7293 4477	26 9 9

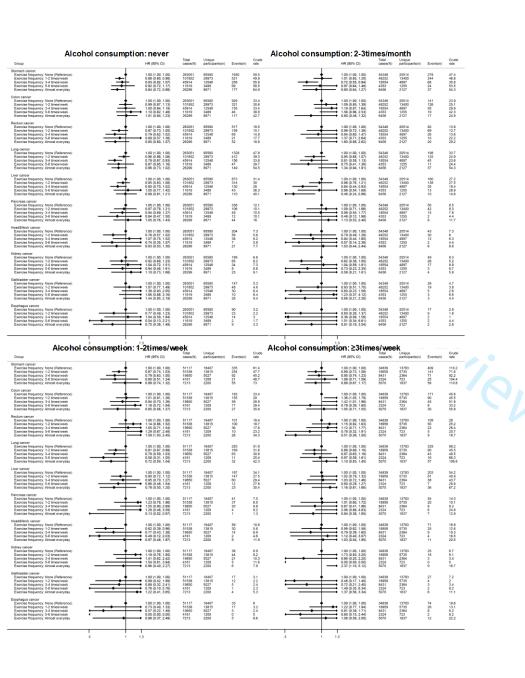
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Group			HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Crude rate			HR (95% CI)	Gases(N)	Unique participants(n)	Events(n)	Cru rate
tomach cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		+	1.00 (1.00, 1.00) 0.89 (0.82, 0.96) 0.84 (0.76, 0.94) 0.92 (0.76, 1.11) 0.89 (0.79, 1.01)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	2325 937 384 111 282	62.4 48.7 49.1 58.8 70.2			1.00 (1.00, 1.00) 1.00 (0.84, 1.15 1.00 (0.80, 1.23) 0.99 (0.68, 1.46) 0.82 (0.60, 1.15	0 12185 14350 235872 4093 4093 1587 24093 1587 24093	19431 9600 4261 1105 2191	347 223 105 28 46	63.2 64 65.8 68.2 67.8
olon cancer Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/week Exercise frequency: Almost everyday			1.00 (1.00, 1.00) 1.06 (0.96, 1.17) 1.01 (0.88, 1.16) ♦ 1.14 (0.90, 1.45) 1.01 (0.86, 1.18)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	1247 583 247 74 171	33.3 30.2 31.5 39.1 42.4		, 	1.00 (1.00, 1.00) 0.99 (0.77, 1.26) 1.26 (0.94, 1.6 2) 1.11 (0.67, 1.8 9) 0.72 (0.45, 1.15)	nseignem 1707134350 20193 45872 9.93	19431 9600 4261 1105 2191	177 109 67 16 20	32. 31. 41. 38. 29.
sctum cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/week Exercise frequency: Atlmost everyday			1.00 (1.00, 1.00) 0.98 (0.85, 1.12) 0.85 (0.70, 1.03) 1.02 (0.74, 1.41) 0.99 (0.80, 1.23)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	715 327 124 39 96	19.1 16.9 15.8 20.6 23.7		<u> </u>	1.00 (1.00, 1.00 0.85 (0.60, 1.21) 1.02 (0.67, 1.54	2185 04350 \$5872	19431 9600 4261 1105 2191	94 51 30 7 11	17 14. 18. 16. 16.
ng cancer Exercise frequency: 1-2 times/week Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/week Exercise frequency: Atimost everyday	<u>_</u>		1.00 (1.00, 1.00) 0.92 (0.84, 1.01) 0.81 (0.71, 0.92) 0.80 (0.63, 1.02) 0.94 (0.82, 1.08)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	1908 689 258 70 243	51.1 35.7 32.9 36.9 60.3		•	1.00 (1.00, 1.00 0.78 (0.61, 0.98) 0.77 (0.56, 1.09 0.87 (0.51, 1.4 0.84 (0.58, 1.23	02185 04350 05872 1093 1093	19431 9600 4261 1105 2191	230 107 49 15 32	41 30 30 36 46
ver cancer Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 3-6 times/week Exercise frequency: Almost everyday			1.00 (1.00, 1.00) 0.96 (0.86, 1.06) 0.88 (0.77, 1.02) 0.91 (0.71, 1.18) 0.94 (0.80, 1.11)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	1271 588 231 62 159	34 30.4 29.4 32.7 39.4		 ★;	1.00 (1.00, 1.00) 0.92 (0.71, 1.20) 0.69 (0.47, 1.01) 1.06 (0.60, 1.82) 0.83 (0.52, 1.33)	BES) 52185 52185 5872 093 587	19431 9600 4261 1105 2191	152 92 32 13 20	27 26 19 31 29
increas cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: A flowst everyday	-		1.00 (1.00, 1.00) 1.06 (0.88, 1.28) 1.12 (0.88, 1.43) 1.03 (0.66, 1.62) 0.97 (0.73, 1.30)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	415 171 80 20 53	11.1 8.8 10.2 10.5 13.1			A 1.00 (1.00, 1.00) 0.81 (0.53, 1.24 0.58 (0.31, 1.0 0.70 (0.25, 1.9) 0.62 (0.29, 1.34)	2185 2185 5872 093 587	19431 9600 4261 1105 2191	68 34 12 4 7	12 9.7 7.5 9.6 10
ead&Neck cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday			1.00 (1.00, 1.00) 0.77 (0.62, 0.95) 0.88 (0.66, 1.16) 0.57 (0.31, 1.08) ♦ 0.95 (0.69, 1.31)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	338 125 59 10 43	9 6.5 7.5 5.3 10.6			1.00 (1.00, 1.00) 0.72 (0.41, 1.29) 1.18 (0.64, 2.19) 1.59 (0.63, 4.06) 0.72 (0.26, 2.03)	2185 24350 5872 093 587	19431 9600 4261 1105 2191	39 19 14 5 4	7.1 5.4 8.7 12 5.8
Iney cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		- +	1.00 (1.00, 1.00) 0.89 (0.71, 1.11) 1.18 (0.90, 1.55) 1.00 (0.59, 1.72) 1.16 (0.83, 1.63)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	264 120 66 14 39	7.1 6.2 8.4 7.4 9.7	·		1.00 (1.00, 1.00) 1.27 (0.79, 2.00) 0.72 (0.35, 1.517) 0.61 (0.15, 2.55) 0.82 (0.32, 2.10)	02185 4350 15872 15872 15872 15872	19431 9600 4261 1105 2191	37 33 9 2 5	6.1 9.4 5.0 4.8 7.3
Ilbladder cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	-		1.00 (1.00, 1.00) 0.91 (0.69, 1.22) 1.11 (0.78, 1.59) 1.63 (0.96, 2.77) 1.25 (0.86, 1.81)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	200 67 37 15 33	5.3 3.5 4.7 7.9 8.1			1.00 (1.00, 1.00 1.44 (0.73, 2.84 1.06 (0.42, 2.66 0.61 (0.08, 4.66 1.82 (0.72, 4.66	e 852185 34350 205872 2093 2093 2093	19431 9600 4261 1105 2191	19 16 6 1	3.4 4.5 3.7 2.4 8.7
ophagus cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday			1.00 (1.00, 1.00) 0.86 (0.64, 1.15) 0.82 (0.54, 1.25) ● 0.68 (0.30, 1.53) ● 0.98 (0.65, 1.47)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	193 64 26 6 27	5.1 3.3 3.2 6.7			1.00 (1.00, 1.00) 0.79 (0.38, 1.68) 0.51 (0.15, 1.74) 0.00 (0.00, 0.00) 0.27 (0.04, 2.03)	at ⁵²¹⁸⁵ A4350 993 587 587	19431 9600 4261 1105 2191	21 11 3 0 1	3.8 3.1 1.9 0 1.5
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Group	Men	HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Crude rate	Women	by copyright, inc	36/bmjopen-2018-025	Unique participants(n)	Events(n)	Cru rate
omach cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 5-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	++	1.00 (1.00, 1.00) 0.88 (0.82, 0.97) 0.87 (0.78, 0.98) 0.93 (0.76, 1.14) 0.84 (0.73, 0.97)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	1762 893 363 101 228	87.7 58.6 62.5 77.7 90.9		1.00 (1.00, 1.00) 0.95 (0.83, 1.00) 0.87 (0.72, 1.00) 0.92 (0.67, 1.59) 0.96 (0.78, 1.15)	5590713168 73310 035787 19823 20954	83300 23072 10563 3144 7626	910 267 126 38 100	40. 35. 35 38 45.
Jan cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 5-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 1.10 (0.98, 1.24) 1.01 (0.86, 1.18) 1.12 (0.85, 1.47) 0.97 (0.80, 1.18)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	779 500 194 56 122	38.5 32.7 33.2 42.9 48.3		Т.00 (1.00, 1.0 0.94 (0.80, 1.1 1.14 (0.93, 1.3 1.14 (0.81, 1.6 0.94 (0.73, 1.2 0.94 (0.73, 1.2) (0.73, 1.2 0.94 (0.73, 1.2) (0.74) (0.74, 1.2) (0.74) (0.	213168 273310 735787 C9823 D20954	83300 23072 10563 3144 7626	645 192 120 34 69	28. 25. 33. 34 31.
setum cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 1.04 (0.89, 1.21) 0.91 (0.74, 1.13) 0.92 (0.62, 1.36) 1.11 (0.87, 1.41)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	455 285 105 27 79	22.4 18.6 17.9 20.6 31.2		1.00 (1.00, 1.0 0.83 (0.65, 1.0 0.84 (0.63, 1.1 1.16 (0.73, 1.84) 0.69 (0.47, 1.0	0 213168 9 73310 3 5787 0 823 20954	83300 23072 10563 3144 7626	354 93 49 19 28	15. 12. 13. 19 12.
ng cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 5-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.86 (0.78, 0.95) 0.76 (0.66, 0.87) 0.72 (0.55, 0.94) 0.90 (0.78, 1.04)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	1500 602 219 57 207	74.4 39.4 37.5 43.6 82.2		1.00 (1.00, 1.0 1.04 (0.89, 1.2 0.93 (0.74, 1.1 1.04 (0.71, 1.5 0.96 (0.75, 1.2	213168 035787 9823 9823 20954	83300 23072 10563 3144 7626	638 194 88 28 68	28 25 24 28 31
rer cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 6-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.96 (0.86, 1.06) 0.88 (0.75, 1.02) 0.83 (0.62, 1.10) 0.89 (0.74, 1.08)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	987 559 210 50 127	48.8 36.6 36 38.2 50.3		1.00 (1.00, 1.0 0.93 (0.76, 1.1 0.79 (0.59, 1.05) 1.32 (0.88, 1.9 1.05 (0.78, 1.4 1.05 (0.78, 1.4	C 213168 73310 35787 9823 20954	83300 23072 10563 3144 7626	436 121 53 25 52	19 16 14 25 23
increas cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 5-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 1.09 (0.88, 1.35) 1.21 (0.91, 1.59) 0.90 (0.52, 1.58) 0.69 (0.46, 1.03)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	249 140 65 13 27	12.2 9.1 11.1 9.9 10.6		1.00 (1.00, 1.26) 0.93 (0.70, 1.26) 0.75 (0.50, 1.12) 1.07 (0.59, 1.91) 1.26 (0.87, 1.81)	213168 73310 35787 9823 20954	83300 23072 10563 3144 7626	234 65 27 11 33	10 8.0 7.1 11
ad&Neck cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 6-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.74 (0.59, 0.92) 0.87 (0.65, 1.16) 0.68 (0.37, 1.25) 0.94 (0.67, 1.33)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	276 116 55 11 38	13.6 7.6 9.4 8.4 15		0.88 (0.32, 2.9 0.82 (0.41, 1.84) 0.88 (0.32, 2.9 0.82 (0.41, 1.62)	0 0 0 0 0 0 0 0 0 0 0 0 0 0	83300 23072 10563 3144 7626	101 28 18 4 9	4. 3. 5 4 4.
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slibladder cancer Exercise frequency: 1-2 times/week Exercise frequency: 1-2 times/week Exercise frequency: 5-8 times/week Exercise frequency: 5-8 times/week		1.00 (1.00, 1.00) 0.81 (0.56, 1.16) 0.89 (0.55, 1.44) 1.43 (0.72, 2.85) 1.48 (0.95, 2.31)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	101 44 21 9 25	5 2.9 3.6 6.9 9.8		Ar 1.00 (1.00, 1.04) 1.20 (0.83, 1.7 ° 1.33 (0.84, 2.1 ° 1.48 (0.69, 3.1 3) 1.06 (0.61, 1.8 3)	UD213168 73310 9823 9823 20954	83300 23072 10563 3144 7626	118 39 22 7 14	5. 5. 6. 7 6.
ophagus cancer Exercise frequency: 1-2 times/week Exercise frequency: 1-2 times/week Exercise frequency: 5-8 times/week Exercise frequency: 5-8 times/week		1.00 (1.00, 1.00) 0.86 (0.65, 1.15) 0.76 (0.50, 1.16) 0.64 (0.28, 1.45) 0.97 (0.64, 1.45)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	184 68 25 6 27	9 4.4 4.3 4.6 10.6	, ,	1.00 (1.00, 1.0 0.83 (0.36, 1.9 0.93 (0.32, 2.6 0.00 (0.00, 0.0 0.31 (0.04, 2.27)	2025 35787 35797 35787 35787 3579777 357977 357977 357977 357977 357977 3579777 3579777 3579777 35797777777777	83300 23072 10563 3144 7626	30 7 4 0 1	1. .9 1. 0 .5

Supplementary Figure 5. Results from running Cox regression models examining effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequenc gand various incident cancer outcomes. Note: Cox regression models using age as the underlying timescale were adjusted for sex [not in models for effect]

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 BMJ Open modification by sex], body mass index [not in models for effect modification by body mass index], systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of cancer [not in models for effect modification by family history of cancer]. smoking status [not in models for effect modification by smoking status] and alcohol consumption [not in Eno modification by alcohol consumption]. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. P-values for multiplicative terms – stomach cancer (p-value = 0.274), colon cancer (p-value $\frac{1}{2}$), rectum cancer (pvalue = 0.107), lung cancer (p-value = 0.016), liver cancer (p-value = 0.129), pancreas cancer (p-value = 0.016), head & neck cancer (p-value = 0.488), kidney cancer (p-value = 0.285), gallbladder cancer (p-value = 0.970), and es a la cancer (p-value = 0.263) by body mass index; stomach cancer (p-value = 0.699), colon cancer (p-value = 0.932), rectum caite (p-value = 0.610), lung cancer (p-value = 0.492), liver cancer (p-value = 0.405), pancreas cancer (p-value = 0.338), head & nec **£** definer (p-value = 0.562), kidney cancer (p-value = 0.280), gallbladder cancer (p-value = 0.295), and esophagus cancer (p-value = (p-value) by smoking; stomach cancer (p-value = 0.655), colon cancer (p-value = 0.977), rectum cancer (p-value = 0.433), lun liver cancer (p-value = 0.704), pancreas cancer (p-value = 0.711), head & neck cancer (p-value = 1.000) 0.336), gallbladder cancer (p-value = 0.350), and esophagus cancer (p-value = 0.550) by alcohol consuming is stomach cancer (pvalue = 0.996), colon cancer (p-value = 0.399), rectum cancer (p-value = 0.478), lung cancer (p-value = $\frac{3}{2}$ $\frac{3}{27}$), liver cancer (p-value = 0.337), pancreas cancer (p-value = 0.086), head & neck cancer (p-value = 0.712), kidney cancer (p-vatie = 0.319), gallbladder cancer (p-value = 0.766), and esophagus cancer (p-value = 0.098) by family history of cancer; and stomachecancer (p-value = 0.405), colon cancer (p-value = 0.957), rectum cancer (p-value = 0.106), lung cancer (p-value = 0.063), liver cancer $\frac{1}{2}$ p-value = 0.278), pancreas cancer (p-value = 0.265), head & neck cancer (p-value = 0.907), kidney cancer (p-value = 0.967), allbladder cancer (pvalue = 0.548), and esophagus cancer (p-value = 0.256) by sex. Abbreviations: HR – Hazard Ratio; CI - Confidence Intervals

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Exercise and incidence of myocardial infarction, stroke, hypertension, type 2 diabetes and site-specific cancers: A prospective cohort study of 257,854 adults in South Korea.

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 Title: Exercise and incidence of myocardial infarction, stroke, hypertension, type 2 diabetes

and site-specific cancers: A prospective cohort study of 257,854 adults in South Korea.

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Abstract

Objective: The objective of this study was to examine the longitudinal associations of exercise frequency with the incidence of myocardial infarction, stroke, hypertension, type 2 diabetes and 10 different cancer outcomes.

Design: A prospective cohort study.

Setting: Physical examination data linked with the entire South Korean population's health insurance system: from 2002 to 2015

Participants: 257,854 South Korean adults who provided up to 7 repeat-measures of exercise (defined as exercises causing sweat) and confounders.

Primary outcome measures: Each disease incidence was defined using both fatal and nonfatal health records (a median follow-up period of 13 years).

Results: Compared with no exercise category, the middle categories of exercise frequency (3-4 or 5-6 times/week) showed the lowest risk of myocardial infarction (hazard ratio[HR]: 0.79; 95% confidence interval[CI]: 0.70-0.90), stroke (HR: 0.80; 95%CI: 0.73-0.89), hypertension (HR: 0.86; 95%CI: 0.85-0.88), type 2 diabetes (HR: 0.87; 95%CI: 0.84-0.89), stomach (HR: 0.87; 95%CI: 0.79-0.96), lung (HR: 0.80; 95%CI: 0.71-0.91), liver (HR: 0.85; 95%CI: 0.75-0.98) and head & neck cancers (HR: 0.76; 95%CI: 0.63-0.93; for 1-2 times/week), exhibiting J-shaped associations. There was, in general, little evidence of effect modification by body mass index, smoking, alcohol consumption, family history of disease, and sex in these associations.

Conclusions: Moderate levels of sweat-inducing exercise showed the lowest risk of myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancers. Public health and lifestyle interventions should, therefore, promote moderate levels of sweat-causing exercise as a behavioural prevention strategy for non-communicable diseases in a wider population of East Asians.

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Keywords: exercise, non-communicable disease, cohort, epidemiology, cardiovascular disease, hypertension, cancer

Article Summary

Strengths and limitations of this study

- This study is the first to investigate the longitudinal associations of exercise with various cardiovascular disease and cancer incidence using a large-scale cohort dataset of South Korean adults (n=257,854) who provided up to 7 repeated measures of exercise and all confounders in order to minimise the risk of regression dilution.
- A limitation is that no strong inference can be drawn about the exercise-incident disease relationships.
- Findings of this study may not be generalizable to adult populations of other ethnic origins.

Introduction

Prevention and control of non-communicable diseases is a contemporary global public health priority. At present, 40 million deaths per year, which accounts for nearly 70% of total deaths globally, are attributable to non-communicable diseases.^{1,2} Moreover, the number of deaths due to non-communicable diseases, such as cardiovascular disease,³ hypertension,⁴ diabetes⁵ and cancer,⁶ has increased dramatically over the past few decades, although agestandardised cardiovascular disease and cancer rates as well as systolic blood pressure levels⁷ have declined.^{8,9} However, trends in these disease traits have varied across different populations, particularly with less favourable changes observed in East Asian populations compared with Western populations. For example, the prevalence of diabetes¹⁰ has increased more rapidly, while the age-standardised prevalence of cardiovascular disease³

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and systolic blood pressure levels⁷ have fallen less steeply in East Asians in comparison with Westerners.

In addition, adults in East Asia tend to have higher prevalence of physical inactivity,¹¹ which is one of the four target behaviours (including unhealthy diet, tobacco use and harmful use of alcohol) that have been set as the global focus to reduce the risk of non-communicable diseases.¹² The beneficial impacts of increased physical activity on various noncommunicable outcomes have been demonstrated by numerous previous investigations. However, the majority of previous research has been predicated on evidence from Western populations, thereby limiting its application to other populations including East Asians. As such, little is currently known about levels of physical activity including exercise in relation to non-communicable diseases in East Asian populations as compared with Western populations.¹³ Another critical gap in the existing literature is the use of data measured only at a single point in time (i.e., baseline), in which case physical activity or exercise levels are assumed to remain constant over time. This methodology, therefore, precludes the fact that individuals' physical activity or exercise levels change with time, and hence may increase the potential for regression dilution.¹⁴ Furthermore, it is well-known that temporal changes occur in other traditional behavioural and metabolic risk factors for non-communicable diseases. such as adiposity levels,^{15,16} smoking,¹⁷ glucose levels¹⁸ and total cholesterol levels,¹⁹ exhibiting different patterns of changes between East Asian and Western populations. Nevertheless, no previous research of East Asians or Westerners took into account changes in these risk markers in understanding the relationships between physical activity and noncommunicable diseases. Moreover, the dose-response relationship between physical activity and various non-communicable disease outcomes has remained unclear in East Asians. Therefore, the purpose of this research was to explore the dose-response relationships between exercise frequency and various types of incident non-communicable diseases, such as myocardial infarction, stroke, hypertension, type 2 diabetes and site-specific cancers,

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using a large-scale prospective cohort of South Korean adults with multiple repeated measures of exercise frequency and other risk markers.

Methods

Study design and participants

This study is based on data from the National Health Insurance Service - Health Screening (NHIS-HEALS) cohort dataset,²⁰ which is a nationally representative random sample (stratified by 2 groups of sex [males and females], 18 groups of age ranges [less than 1 year, 1-4 years, every 5 years between 5-79 years, and more than 80 years], 3 groups of employment status [insured employees, self-employed individuals and medical aid beneficiaries] and 41 groups of income levels [upper 20% for insured employees, lower 20% for insured self-employed individuals and the lowest level for medical aid beneficiaries]²¹) of over 500,000 South Korean adults aged 40-79 years between 2002 and 2003 made available by the NHIS. The NHIS is a single health insurance system in South Korea, which manages and maintains information on the entire South Korean population's healthcare utilization; it is mandatory for all South Koreans to take part in the national health insurance system. The NHIS is also responsible for maintaining national health examination programs involving data from general health examinations of all insured employees, self-employed individuals and medical aid beneficiaries aged over 40 years; it is recommended for them to perform the health examination at least every two years. The health examination involves collection of information on body composition, blood profiles, blood pressure, self-reported lifestyles, self-reported physician-diagnosed disease, and self-reported family history of disease.

The NHIS-HEALS cohort includes a wide variety of information collected between 2002 and 2015: health examination data and demographic and eligibility data (e.g., in-patient and outpatient hospital records, medical bill, health insurance and medical aid beneficiaries). In the present analysis, we utilised health examination data collected between 2002 and 2008 to define the exercise frequency and all confounders. There was a change in the type of self-

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report methods in 2009; hence, health examination data collected in or after 2009 were not considered in the analysis due to the inability to harmonise variables. However, we used full follow-up data accrued from 2002 until 2015. This research was approved by the Institutional Review Board (4-2017-0051) of the Yonsei University's Severance Hospital in Republic of Korea.

Exposure

The primary exposure variable of this study was exercise frequency, assessed using guestionnaires administered during the health examinations. The specific guestion asked was "How many times per week do you engage in exercise that causes sweating?" Participants were asked to choose only one of the following 5 possible answers: None, 1-2 times/week, 3-4 times/week, 5-6 times/week and almost every day.

Outcomes

In the present study, we evaluated 14 incident disease outcomes, namely, myocardial infarction; stroke, hypertension; type 2 diabetes mellitus; and stomach, colon, rectum, lung, liver, head & neck, pancreatic, kidney, gall bladder and esophagus cancers. Participants' inpatient and out-patient hospital records (i.e., non-fatal status) and death records (i.e., fatal status) obtained through linkage with Statistics Korea were both classified according to the International Classification of Disease (ICD)-10 codes to classify different incidence types (Supplementary Table 1). Additionally, blood pressure (e.g., systolic ≥140 mm Hg, diastolic \geq 90 mm Hg) and fasting glucose levels (e.g., \geq 126 mg/dL), both of which were measured during physical examinations, were used in conjunction with physicians' diagnosis information and ICD-10 codes to define incident hypertension and type 2 diabetes, respectively. Each incident disease outcome was defined as the first occurrence of either non-fatal or fatal respective disease cases. Incident disease cases were adjudicated using hospital and death records collected through December 31st, 2015. The median follow-up was 13.0 years (interguartile range: 10.2-11.3 years)

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Other covariates

The following covariates were included as confounders in the analyses: sex, body mass index (weight in kilograms (kg) divided by height in meters squared (m²)), systolic blood pressure, fasting glucose, total cholesterol, family history of heart disease, stroke or hypertension [only in models for incident myocardial infarction, stroke or hypertension], family history of diabetes [only in models for type 2 diabetes], family history of cancer [only in models for incident cancer outcomes], smoking status (never, previously, currently) and alcohol consumption (never, 2-3 times/month, 1-2 times/week, \geq 3 times/week).

Statistical analysis

Analyses were performed to summarise descriptive statistics (e.g., means, standard deviations, frequency, and proportions) of each covariate and incident disease outcome for all participants and by exercise frequency category. Cox regression with age as the underlying time scale was used to estimate the associations of exercise frequency with each incident disease outcome, with adjustment for all the above-mentioned confounders as well as without any adjustment. Hazard ratios along with corresponding 95% confidence intervals were calculated to evaluate relative risk of each incident disease outcome. Data were structured to enable the inclusion of exercise frequency and all confounders from both baseline and up to 6 repeated measures as time-updated covariates. This approach takes into account changes in exercise frequency as well as each confounder over time in relation to disease incidence. Individuals who reported no exercise served as a reference group for all comparisons. Effect modification by body mass index (<25, \geq 25kg²/m), smoking status, alcohol consumption, family history of disease and sex was also examined based on Wald tests of interaction terms in the fully adjusted models for each incident disease outcome. Visual inspections of log-log plots provided support for the assumptions of proportional hazards for all covariates. A sensitivity analysis where incident disease cases occurring during the first 2 years of follow-up were removed was performed to address reverse

causality. Analyses were performed in Stata/SE Version 14 (StataCorp LP, College Station, TX).

Patient and Public Involvement.

 Neither patients nor members of the public were involved in this study.

Results

Of an initial sample of 512,190 individuals, 74,931 had missing data on at least one of the model covariates, and 179,405 had self-reported physician-diagnosed heart attack, stroke, hypertension (additionally, systolic \geq 140 mm Hg or diastolic \geq 90 mm Hg), diabetes (additionally, fasting glucose levels \geq 126 mg/dL) or cancer at baseline, respectively. Excluding these individuals resulted in a final sample for analysis of 257,854 individuals (Figure 1).

Individuals provided up to 7 measures of exercise frequency and each confounder (i.e., baseline plus 6 repeated measures). Participants' characteristics at baseline are summarised in Table 1. Supplementary Table 2 summarises participants' characteristics at each repeat assessment. Individuals in the categories of 1-2, 3-4 or 5-6 times/week of exercise were slightly younger, but showed higher proportions of family history of disease and lower proportions of never smoking or drinking alcohol, compared with those in the categories of none or almost every day of exercise. Across the seven time points (Supplementary Figure 1), the proportion of individuals who reported no exercise decreased while the proportion who reported 1-2 or 3-4 times/week of exercise increased; there were no noticeable changes for the categories of 5-6 times/week or almost every day of exercise.

Overall, J-shaped associations were found between exercise frequency and incident myocardial infarction, stroke, hypertension and type 2 diabetes. Hazard ratios for these diseases were lowest in the middle categories of exercise frequency (e.g., 3-4 or 5-6 times/week) (Figure 2). There were no associations for the most frequent exercise category

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 (e.g., almost every day) with the incidence of myocardial infarction, stroke and type 2 diabetes.

J-shaped associations were also found for incident stomach, lung, liver and head & neck cancers (Figure 3). Higher exercise frequencies (e.g., 1-2, 3-4 times/week and almost every day) were associated with lower hazards of incident stomach cancer. No statistical significance was observed for incident colon, rectum, pancreas, kidney, gallbladder and esophagus cancers. Crude event rates per 100,000 person-years in the middle categories of exercise frequency were relatively lower for incident rectum, and esophagus cancers, but higher for incident pancreas, kidney and gallbladder cancers. Cox regression models with no adjustment for confounders (Supplementary Figure 2) and a sensitivity analysis (Supplementary Figure 3) in which incident cases occurring in the first 2 years of follow-up were removed both revealed nearly identical patterns of associations as the main analyses.

Figure 4 shows comparisons of results that showed statistical significance for multiplicative interaction terms between exercise frequency and each incident disease outcome. Strong J-shaped associations for incident hypertension were identified at each level of body mass index. J-shaped associations of exercise frequency with incident hypertension were strong only in the more favourable levels of smoking (e.g., never, previously) and alcohol consumption (e.g., never, 2-3 times/month, 1-2 times/week); no or weak associations were identified in the most harmful level of smoking (e.g., current smokers) and alcohol consumption (e.g., \geq 3 times/week). J-shaped associations were evident at all levels of family history of CVD and sex for incident hypertension, and sex for incident type 2 diabetes. Exercise frequency was associated with incident lung cancer in non-obese individuals, but there was no evidence of association in obese individuals. All comparisons stratified by each potential effect modifier are presented in Supplementary Figures 4 and 5.

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Discussion

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This is the first investigation examining the prospective associations of exercise with various incident non-communicable disease outcomes using multiple repeated measures of covariates in East Asian populations. We identified J-shaped associations of sweat-inducing exercise with incident myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancers, with the greatest benefits being observed in the middle categories of exercise frequency (e.g., 3-4 or 5-6 times/week): 1-2 times/week for head & neck cancer. These findings provide two important clinical and public health implications. First, prevention and management of non-communicable diseases in East Asians may benefit considerably from employing an exercise promotion approach in the context of combined non-communicable disease prevention. Mechanism research indicates that cardiovascular disease and type 2 diabetes have similar biological pathways relating to exercise,^{22,23} so an integrated prevention approach can be applied to control and manage these two diseases at a minimum.⁵ Moreover, regular participation in exercise can induce favourable changes in intermediate cardiometabolic risk markers,²⁴ which are important predictors of typical non-communicable diseases. Hence, promoting exercise has great potential to act as an integrative behavioural strategy for preventing and controlling various non-communicable diseases simultaneously in East Asian populations.

Second, individuals who engage in exercise 3-4 or 5-6 times/week, rather than every day, may be able to reduce their risk of developing myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung and liver cancers: 1-2 times/week for head & neck cancer. Similar J-shaped associations between high intensity exercise (e.g., running) and cardiovascular disease risk have also been reported in previous cohort studies of Western^{25,26} and Japanese adults.²⁷ Nevertheless, the present study as well as previous research²⁵⁻²⁷ found that the risk of developing cardiovascular events in individuals who had the highest level of exercise was not noticeably higher compared with those who had the lowest level of exercise. No previous research in East Asians has found such J-shaped relationships between exercise or physical activity and other incident disease outcomes such as hypertension,²⁸⁻³² diabetes³³⁻⁴⁰ and different type of cancers.⁴¹⁻⁴⁷ However, previous meta-

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analyses of cohort studies comprising predominantly Westerners found leisure-time physical activity to have curvilinear (but not J-shaped) associations with the incidence of type 2 diabetes,⁴⁸ and linear associations with the incidence of hypertension⁴⁹ and various site-specific cancers (liver, lung, head & neck, kidney, colon, rectal, bladder, gastric cardia, breast, endometrial, myeloid leukemia, myeloma, esophageal adenocarcinoma).⁵⁰ While additional research is needed to confirm the J-shaped associations of exercise with various incident diseases in other samples of East Asians, findings of this research provide a strong rationale for development and implementation of public health policies and clinical trials aimed at promoting a moderate level of sweat-causing exercise to minimise the risk of myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancers.

Another finding of this research is that associations of sweat-inducing exercise with hypertension were modified by body mass index, smoking, alcohol consumption, family history of cardiovascular disease and sex: lung cancer by body mass index and type 2 diabetes by sex. Notably, exercise frequency was not associated with hypertension in individuals who are smokers or drinking alcohol \geq 3 times/week (except for 3-4 times/week of exercise). This observation provides some evidence that the harmful impacts of smoking or binge drinking on hypertension⁵¹⁻⁵³ may not be offset completely by exercise. This, in turn, appears to advocate for the need for implementing a combined hypertension prevention strategy targeting promotion of exercise in conjunction with smoking cessation and reductions in alcohol consumption in East Asians.¹³ For lung cancer, the null associations in individuals with body mass index \geq 25 may be indicative of potential residual confounding through reported bias in smoking behaviours. Nonetheless, there was little evidence for effect modification for other disease comparisons, highlighting the importance of promoting exercise for the prevention of various non-communicable diseases in individuals at different levels of body mass index, smoking, alcohol consumption, family history of disease and sex.

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This study has several notable strengths. First, we used data from a large prospective cohort study in which exercise and other risk markers were assessed on multiple occasions (up to 7 times). Nearly 84% and 5% of the full participants provided 1 and 6 repeated measures of all covariates, respectively. Compelling evidence indicates that the risk of regression dilution can be reduced using repeated measures of exposure and confounders.¹⁴ Moreover, we examined the dose-response relationship of exercise frequency with a wide variety of specific types of incident non-communicable disease outcomes simultaneously using inpatient and out-patient diagnosis data as well as mortality data. The large sample size (n=257,854) is another strength.

This study has some limitations. Findings of this study may not be generalizable to adult populations of other ethnic origins. Due to the observational nature of this research, no strong inference can be drawn about the exercise-incident disease relationships. In addition, the accuracy of hospital admission records is uncertain, although the accuracy of death records from Statistics Korea was found to be 92% in previous research.⁵⁴ No information about medication use was available in the cohort data, so we could not use it as a potential confounder and another condition when defining disease status (e.g., hypertension, type 2 diabetes) at both baseline and follow-up. Furthermore, no exercise duration was assessed; hence, inference was made purely based on exercise frequency. Moreover, ICD-10 codes for sex-specific cancers (e.g., prostate and breast cancers) were masked due to the data management policy set forth by the NHIS, so it was not possible to examine such cancers in the present study. The lack of data on diet, which is another behavioural risk marker for noncommunicable diseases¹² is another limitation. Moreover, a sizeable proportion (n=74,931; 14.6%) of individuals were excluded due to the missing information on the covariates. Another limitation is that the measurement methods to assess the covariates were not standardized across the different medical institutes participating in the NHIS-HEALS cohort.

Conclusion

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Individuals who engaged in sweat-inducing exercise around 3-6 times/week (as opposed to every day) generally had the lowest risk of developing myocardial infarction, stroke, hypertension, type 2 diabetes, stomach, lung, liver and head & neck cancers. These findings were generally applicable to different sub-populations as stratified by body mass index, smoking, alcohol consumption, family history of disease, and sex. Public health and lifestyle interventions should promote a moderate level of sweat-inducing exercise as a behavioural strategy for prevention and control of non-communicable diseases in a wider population of East Asians.

Author Contributions

YK designed this study, performed statistical analysis, and drafted an initial version of the manuscript. SJS, SMH and SHJ all contributed to conceptualizing the study idea and developing the analytical plans, and provided assistance with statistical analysis. All authors critically reviewed, approved of the final version of the manuscript, and agreed to be responsible for all facets of this work.

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Conflicts of interest

None declared.

Patient consent

Not required.

Ethics approval

This research was approved by the Institutional Review Board (4-2017-0051) of the Yonsei University's Severance Hospital in Republic of Korea.

Data sharing statement

Data sharing is not applicable because no informed consent for data sharing was obtained TOPPE KELICA ONL

from the participants.

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54		Figure Logonde
55 56		Figure Legends
57	Figur	e 1. A flow diagram. Note: "N" indicates numbers of total observations (i.e. participants
58	-	provided repeated measures are treated as separate observations) and "n" indicates
59		bers of unique participants at baseline. Data without missingness and prevalence of major
60		ses were used to create final analysis datasets for different incident disease outcomes;

while the number of unique participants at baseline is the same for all incident disease outcomes, the total number of observations varied due to the nature of time-updated covariate analyses (i.e. censoring of subsequent time-updated covariates when an incident disease case occurs before the end date of repeated measures). Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million South Korean adults (2002-2015) with the entire South Korean population's health insurance system.

Figure 2. Associations of exercise frequency with various incident cardiovascular disease outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of heart disease, stroke or hypertension (in models for myocardial infarction, stroke and hypertension) or diabetes (in models for Type 2 diabetes), smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million Korean adults (2002-2015) with the entire South Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

Figure 3. Associations of exercise frequency with various incident cancer outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of cancer, smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million South Korean adults (2002-2015) with the entire South Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

Figure 4. Results from assessment of effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequency and each incident disease outcome. Only associations for which the multiplicative interaction terms were statistically significant are presented. Cox regression models with age as the underlying timescale were adjusted for sex [not in models for effect modification by sex], body mass index [not in models for effect modification by body mass index], systolic blood pressure, fasting glucose levels, total cholesterol levels, family history [not in models for effect modification by family history of respective disease] of heart disease/stroke/hypertension (in models for myocardial infarction, stroke and hypertension), diabetes (in models for Type 2 diabetes) or cancer (in models for each cancer), smoking status [not in models for effect modification by smoking status] and alcohol consumption [not in models for effect modification by alcohol consumption]. Crude rates are per 100,000 personyears. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. P-values for multiplicative interactions with exercise frequency are as follows; Outcome – hypertension: body mass index (0.049), smoking (<0.001), alcohol consumption (<0.001), family history of cardiovascular disease (0.029) and sex (<0.001); Outcome - lung cancer: body mass index (0.016), and; Outcome - type 2 diabetes: sex (0.012). Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million South Korean adults (2002-2015) with the entire South

Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

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Variables	All (n=257,854)					
		None (n=148,284)	1-2 times/week (n=62,923)	3-4 times/week (n=24,836) б па	5-6 times/week (n=6,676)	Almost every (n=15,135)
Sex, %		(11-140,204)	(11-02,020)	Sc	(11-0,070)	(11-10,100)
Men	50.5%	43.8%	63.3%	57.5% ਰੋਟਿੱ	52.9%	49.6%
Women	49.5%	56.2%	36.7%	42.5%	47.1%	50.4%
Age, years	50.7 (8.7)	51.5 (9.2)	49.0 (7.5)	42.5% at 07 49.3 (7.5) ed m 9	49.9 (7.8)	53.5 (9.3)
Body Mass Index, kg ² /m	23.5 (2.8)	23.3 (2.9)	23.6 (2.7)	237 (26) 🕁 🗹 🗖	23.7 (2.6)	23.7 (2.7)
Systolic blood pressure, mm Hg	116.8 (11.2)	116.6 (11.3)	117.1 (11.0)	116.8 (11.1)	116.8 (11.2)	117.3 (11.3)
Diastolic blood pressure, mm Hg	73.4 (7.9)	73.1 (8.0)	73.8 (7.8)	73.5 (7.9)	73.4 (8.0)	73.4 (7.9)
Fasting glucose levels, mg/dL	90.2 (12.3)	90.1 (12.4)	90.4 (12.2)	89.9 (11.9) 😐 🙆 💊	90.2 (12.3)	90.2 (12.4)
Total cholesterol, mg/dL	197.0 (36.7)	196.5 (37.1)	197.7 (36.2)	116.8 (11.1) to nt with 73.5 (7.9) to period 197.8 (35.9) to period 197.8 (35.9) to period 15.9% to period 17.2% to period 17.	197.8 (36.1)	197.4 (36.8)
Family history of heart disease, stroke or hypertension, %	12.2%	10.8%	13.9%	<u>15.9% </u>	16.5%	10.9%
Family history of cancer, %	14.2%	13.1%	15.3%	<u>17.2%</u> <u>a</u> a a	16.6%	14.5%
Family history of diabetes, %	6.3%	5.4%	7.2%		9.2%	5.7%
Smoking status, %				65.2% nn g		
Never	68.1%	71.9%	59.1%		68.8%	71.7%
Previously	8.4%	5.8%	12.0%		12.5%	8.8%
Currently	23.6%	22.2%	28.9%	22.1% A	18.8%	19.5%
Alcohol Consumption, % Never	58.4%	64.5%	47.6%	50.5% trai i	52.2%	59.3%
2-3 times/month	16.4%	13.8%	21.3%		18.8%	14.1%
1-2 times/week	15.8%	12.4%	22.0%	<u>19.7%</u> <u>5</u> 20.2% <u>9</u>	18.1%	14.5%
≥3 times/week	9.5%	9.3%	9.1%	9.5% an	10.8%	12.1%
Incident myocardial infarction, n (%)	3,047 (1.2)	1,741 (1.2)	723 (1.1)	276 (1.1)	88 (1.3)	219 (1.4)
Incident stroke, n (%)	16,134 (6.3)	9,689 (6.5)	3,333 (5.3)	1,482 (6.0) 🖺	390 (5.8)	1,240 (8.2)
Incident hypertension, n (%)	120,203 (46.6)	65,964 (44.5)	30,623 (48.7)	12,617 (50.8) 9	3,294 (49.3)	7,705 (50.9)
Incident Type 2 diabetes, n (%)	50,459 (19.6)	27,128 (18.3)	10,666 (6.5)	5,421 (21.8	1,399 (21.0)	3,285 (21.7)
Incident stomach cancer, n (%)	4,788 (1.9)	2,672 (1.8)	13,226 (21.0)	489 (2.0) 😴 🖣	139 (2.1)	328 (2.2)
Incident colon cancer, n (%)	2,711 (1.1)	1,424 (1.0)	1,160 (1.8)	489 (2.0) te une 314 (1.3) Cf une	90 (1.3)	191 (1.3)
Incident rectum cancer, n (%)	1,494 (0.6)	809 (0.6)	692 (1.1)	154 (0.6)	46 (0.6)	107 (0.7)
Incident lung cancer, n (%)	3,601 (1.4)	2,138 (1.4)	796 (1.3)	314 (1.3) C ne 154 (0.6) n 8 307 (1.2) 0 20	85 (1.3)	275 (1.8)
Incident liver cancer, n (%)	2,620 (1.0)	1,423 (1.0)	680 (1.1)	263 (1.1) G N 92 (0.4) S a	75 (1.1)	179 (1.2)
Incident pancreas cancer, n (%)	864 (0.3)	483 (0.3)	205 (0.3)		24 (0.4)	60 (0.4)
Incident head & neck cancer, n (%)	656 (0.3)	377 (0.3)	144 (0.2)	73 (0.3)	15 (0.2)	47 (0.3)
Incident kidney cancer, n (%)	589 (0.2)	301 (0.2)	153 (0.2)	75 (0.3)	16 (0.2)	44 (0.3)
Incident gallbladder cancer, n (%)	400 (0.2)	219 (0.1)	83 (0.1)	43 (0.2)	16 (0.2)	39 (0.3)
Incident esophagus cancer, n (%)	352 (0.1)	214 (0.1)	75 (0.1)	29 (0.1) 6	6 (0.09)	28 (0.2)
Median follow-up period, years	13.0 (12.2, 13.3)	13.0 (12.2, 13.3)	13.0 (12.2, 13.3)	13.0 (12.2, 13.3) B . S	12.7 (12.2, 13.3)	12.6 (12.2, 1
(interquartile range)	·			bi ographique de l		

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1 2 3 4 5 6 7 8 9	Note: Values presented are means unless indicated as an 'n'. Values in parentheses are standard deviations unless otherwise indicated. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million South Korean adulta (2002, 2015) with the entire South Korean penulation's health insurance system
10 11 12 13 14 15 16 17 18	addits (2002-2015) with the entitle South Kolean population's health histifance system.
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			Total	Unique		Crud
Group		HR (95% CI)	cases(N) participants	s(n) Events(r	n) rate
Ayocardial infarction						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	1741	40.6
Exercise frequency: 1-2 times/week		0.87 (0.80, 0.95)	220601	62923	723	31.7
Exercise frequency: 3-4 times/week	-	0.79 (0.70, 0.90)	92749	24836	276	29.2
Exercise frequency: 5-6 times/week	•	- 0.98 (0.79, 1.22)	22457	6676	88	38.2
Exercise frequency: Almost everyday	•	0.94 (0.82, 1.09)	45038	15135	219	46.4
Stroke						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	9689	232
Exercise frequency: 1-2 times/week	-	0.86 (0.82, 0.89)	220601	62923	3333	149
Exercise frequency: 3-4 times/week		0.83 (0.79, 0.88)	92749	24836	1482	160
Exercise frequency: 5-6 times/week	.	0.80 (0.73, 0.89)	22457	6676	390	173
Exercise frequency: Almost everyday		0.95 (0.90, 1.01)	45038	15135	1240	272
Hypertension						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	65964	238
Exercise frequency: 1-2 times/week	•	0.92 (0.90, 0.93)	220601	62923	30623	21
Exercise frequency: 3-4 times/week		0.86 (0.85, 0.88)	92749	24836	12617	207
Exercise frequency: 5-6 times/week	-	0.87 (0.84, 0.90)	22457	6676	3294	219
Exercise frequency: Almost everyday	+	0.95 (0.93, 0.97)	45038	15135	7705	26
Γype 2 diabetes						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	27128	145
Exercise frequency: 1-2 times/week	+	0.92 (0.90, 0.94)	220601	62923	13226	167
Exercise frequency: 3-4 times/week	-	0.87 (0.84, 0.89)	92749	24836	5421	174
Exercise frequency: 5-6 times/week	⊢	0.88 (0.84, 0.93)	22457	6676	1399	168
Exercise frequency: Almost everyday	-	0.97 (0.93, 1.00)	45038	15135	3285	173
I .3	1	1.3				

Figure 2. Associations of exercise frequency with various incident cardiovascular disease outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of heart disease, stroke or hypertension (in models for myocardial infarction, stroke and hypertension) or diabetes (in models for Type 2 diabetes), smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million Korean adults (2002-2015) with the entire South Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

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Group	HR	(95% CI)	Total cases(N)	Unique participants(n)	Events(n)
Stomach cancer		. (1 00 1 00)	403356	148284	2672
Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week		0 (1.00, 1.00)	220601	62923	1160
Exercise frequency: 3-4 times/week		7 (0.79, 0.96)	92749	24836	489
Exercise frequency: 5-6 times/week		3 (0.78, 1.10)	22457	6676	139
Exercise frequency: Almost everyday	0.88	3 (0.78, 0.98)	45038	15135	328
Colon cancer					
Exercise frequency: None (Reference)		0 (1.00, 1.00)	403356	148284	1424
Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week		5 (0.95, 1.15) 5 (0.93, 1.20)	220601 92749	62923 24836	692 314
Exercise frequency: 5-6 times/week		4 (0.92, 1.41)	22457	6676	314 90
Exercise frequency: Almost everyday		7 (0.83, 1.12)	45038	15135	191
Rectum cancer					
Exercise frequency: None (Reference)		0 (1.00, 1.00)	403356	148284	809
Exercise frequency: 1-2 times/week		6 (0.85, 1.09)	220601	62923 24836	378
Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week		3 (0.74, 1.05) 0 (0.74, 1.35)	92749 22457	24836 6676	154 46
Exercise frequency: Almost everyday		5 (0.74, 1.35) 5 (0.78, 1.16)	45038	15135	107
Lung cancer					
Exercise frequency: None (Reference)		0 (1.00, 1.00)	403356	148284	2138
Exercise frequency: 1-2 times/week		0 (0.83, 0.98)	220601	62923	796
Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week		0 (0.71, 0.91) 1 (0.65, 1.01)	92749 22457	24836 6676	307 85
Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1 (0.65, 1.01) 3 (0.82, 1.05)	45038	15135	275
Liver cancer					
Exercise frequency: None (Reference)		0 (1.00, 1.00)	403356	148284	1423
Exercise frequency: 1-2 times/week		5 (0.87, 1.05)	220601	62923	680
Exercise frequency: 3-4 times/week		5 (0.75, 0.98)	92749	24836 6676	263
Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		4 (0.74, 1.18) 3 (0.79, 1.08)	22457 45038	15135	75 179
Pancreas cancer	•	(0.70, 1.00)	40000	10100	
Exercise frequency: None (Reference)	1.00	0 (1.00, 1.00)	403356	148284	483
Exercise frequency: 1-2 times/week	1.02	2 (0.86, 1.20)	220601	62923	205
Exercise frequency: 3-4 times/week	1.01	1 (0.81, 1.27)	92749	24836	92
Exercise frequency: 5-6 times/week		7 (0.64, 1.46)	22457	6676	24
Exercise frequency: Almost everyday	0.92	2 (0.70, 1.20)	45038	15135	60
Head&Neck cancer Exercise frequency: None (Reference)	1.00	0 (1.00, 1.00)	403356	148284	377
Exercise frequency: 1-2 times/week		5 (0.63, 0.93)	220601	62923	144
Exercise frequency: 3-4 times/week		2 (0.71, 1.19)	92749	24836	73
Exercise frequency: 5-6 times/week		3 (0.43, 1.22)	22457	6676	15
Exercise frequency: Almost everyday	0.92	2 (0.68, 1.25)	45038	15135	47
Kidney cancer Exercise frequency: None (Reference)	1.00	0 (1.00, 1.00)	403356	148284	301
Exercise frequency: 1-2 times/week		5 (0.78, 1.17)	220601	62923	153
Exercise frequency: 3-4 times/week		0 (0.85, 1.42)	92749	24836	75
Exercise frequency: 5-6 times/week	→ 0.93	3 (0.56, 1.54)	22457	6676	16
Exercise frequency: Almost everyday	→ 1.11 → 1.11	1 (0.81, 1.52)	45038	15135	44
Gallbladder cancer Exercise frequency: None (Reference)	1.07	0 (1.00, 1.00)	403356	148284	219
Exercise frequency: 1-2 times/week		3 (0.75, 1.27)	220601	62923	83
Exercise frequency: 3-4 times/week		9 (0.78, 1.52)	92749	24836	43
Exercise frequency: 5-6 times/week	1.47	7 (0.88, 2.45)	22457	6676	16
Exercise frequency: Almost everyday		0 (0.93, 1.84)	45038	15135	39
Esophagus cancer		0 (1 00 1 00)	402250	140004	214
Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week		0 (1.00, 1.00) 6 (0.65, 1.12)	403356 220601	148284 62923	214 75
Exercise frequency: 1-2 times/week		B (0.65, 1.12) B (0.52, 1.15)	92749	24836	29
Exercise frequency: 5-6 times/week		7 (0.25, 1.29)	22457	6676	6
Exercise frequency: Almost everyday		0 (0.60, 1.33)	45038	15135	28

Figure 3. Associations of exercise frequency with various incident cancer outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of cancer, smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million South Korean adults (2002-2015) with the entire South Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

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Group		HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Crude rate
Hypertension: Non-cbess (BMI-25) Exercise frequency: None (Reference) Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: 4-1 dimes/week	**	$\begin{array}{c} 1.00 & (1.00, 1.00) \\ 0.92 & (0.91, 0.94) \\ 0.85 & (0.83, 0.87) \\ 0.86 & (0.82, 0.90) \\ 0.95 & (0.92, 0.98) \end{array}$	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2383 2114.3 2079.8 2199.5 2653.7
Hypertension: Obese (BMI225) Exercise frequency: None (Reference) Exercise frequency: 3-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: 3-4 most everyday	≠	1.00 (1.00, 1.00) 0.93 (0.90, 0.95) 0.91 (0.88, 0.94) 0.92 (0.87, 0.98) 0.98 (0.94, 1.02)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2383 2114.3 2079.8 2199.5 2653.7
Hypertension: Smoking - Never Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	***	$\begin{array}{c} 1.00 & (1.00, 1.00) \\ 0.89 & (0.88, 0.91) \\ 0.82 & (0.81, 0.84) \\ 0.86 & (0.82, 0.89) \\ 0.93 & (0.90, 0.95) \end{array}$	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2383 2114.3 2079.8 2199.5 2653.7
Hypertension: Smoking - Previously Exercise frequency: (Nene (Reference) Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: 4-1 dimes/week	≠	1.00 (1.00, 1.00) 0.91 (0.87, 0.95) 0.88 (0.83, 0.93) 0.87 (0.79, 0.96) 0.96 (0.88, 1.04)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2383 2114.3 2079.8 2199.5 2653.7
Hypertension: Smoking - Currently Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.98 (0.95, 1.01) 0.97 (0.93, 1.01) 0.95 (0.88, 1.03) 1.03 (0.97, 1.09)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2383 2114.3 2079.8 2199.5 2653.7
Hypertension: Alcohol consumption - Never Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	≠ •	$\begin{array}{c} 1.00 & (1.00, 1.00) \\ 0.90 & (0.88, 0.92) \\ 0.84 & (0.81, 0.86) \\ 0.84 & (0.80, 0.88) \\ 0.93 & (0.90, 0.96) \end{array}$	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2383 2114.3 2079.8 2199.5 2653.7
Hypertension: Alcohol consumption -2-3 times/month Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: 5-6 times/week	++	1.00 (1.00, 1.00) 0.92 (0.89, 0.96) 0.84 (0.80, 0.88) 0.91 (0.84, 0.99) 1.01 (0.95, 1.08)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2383 2114.3 2079.8 2199.5 2653.7
Hypertension: Alcohol consumption - 1-2 times/week Exercise frequency: None (Reference) Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: 4-1 dimost everyday	₹	1.00 (1.00, 1.00) 0.91 (0.88, 0.94) 0.91 (0.87, 0.95) 0.91 (0.84, 0.99) 0.96 (0.91, 1.03)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2383 2114.3 2079.8 2199.5 2653.7
Hypertension: Alcohol consumption - 23 times/week Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.98 (0.94, 1.02) 0.92 (0.87, 0.97) 0.93 (0.85, 1.03) 0.99 (0.92, 1.05)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2383 2114.3 2079.8 2199.5 2653.7
Hypertension: Men Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Atimost everyday		1.00 (1.00, 1.00) 0.94 (0.93, 0.96) 0.92 (0.90, 0.94) 0.93 (0.88, 0.97) 1.00 (0.97, 1.03)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2383 2114.3 2079.8 2199.5 2653.7
Hypertension: Women Exercise frequency: None (Reference) Exercise frequency: 4-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	±+++	$\begin{array}{c} 1.00 & (1.00, 1.00) \\ 0.87 & (0.85, 0.89) \\ 0.79 & (0.76, 0.81) \\ 0.82 & (0.78, 0.87) \\ 0.91 & (0.88, 0.95) \end{array}$	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	65964 30623 12617 3294 7705	2383 2114.3 2079.8 2199.5 2653.7
Type 2 diabetes: Men Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	≠	$\begin{array}{c} 1.00 & (1.00, 1.00) \\ 0.91 & (0.89, 0.94) \\ 0.87 & (0.84, 0.90) \\ 0.88 & (0.82, 0.94) \\ 0.93 & (0.88, 0.98) \end{array}$	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	27128 13226 5421 1399 3285	1457.6 1671.1 1745 1681.1 1737.5
Type 2 diabetes: Women Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	±	1.00 (1.00, 1.00) 0.91 (0.88, 0.95) 0.86 (0.82, 0.90) 0.90 (0.83, 0.98) 1.03 (0.97, 1.08)	403356 220601 92749 22457 45038	148284 62923 24836 6676 15135	27128 13226 5421 1399 3285	1457.6 1671.1 1745 1681.1 1737.5
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Figure 4. Results from assessment of effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequency and each incident disease outcome. Only associations for which the multiplicative interaction terms were statistically significant are presented. Cox regression models with age as the underlying timescale were adjusted for sex [not in models for effect modification by sex], body mass index [not in models for effect modification by body mass index], systolic blood pressure, fasting glucose levels, total cholesterol levels, family history [not in models for effect modification by family history of respective disease] of heart disease/stroke/hypertension (in models for myocardial infarction, stroke and hypertension), diabetes (in models for Type 2 diabetes) or cancer (in models for each cancer), smoking status [not in models for effect modification by smoking status] and alcohol consumption [not in models for effect modification by alcohol consumption]. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. P-values for multiplicative interactions with exercise frequency are as follows; Outcome hypertension: body mass index (0.049), smoking (<0.001), alcohol consumption (<0.001), family history of cardiovascular disease (0.029) and sex (<0.001); Outcome - lung cancer: body mass index (0.016), and; Outcome - type 2 diabetes: sex (0.012) - - - - Data were obtained from a prospective cohort, which has been established by linking physical examination data of over half a million South Korean adults (2002-

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3	2015) with the entire South Kerean population's health insurance system. Abbreviations: HP - Hazard Paties
4	2015) with the entire South Korean population's health insurance system. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals
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Incident disease outcome	Definition
Myocardial infarction	ICD 10 codes I21-I23
Stroke	ICD 10 codes I60-I64
Hypertension	ICD 10 codes I10, I11 and I15, systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or physician diagnosis
Type 2 diabetes	ICD 10 codes E11, fasting glucose ≥126 mg/dL, or physician diagnosis
Stomach cancer	ICD 10 codes C16
Colon cancer	ICD 10 codes C18
Rectum cancer	ICD 10 codes C20
Lung cancer	ICD 10 codes C34
Liver cancer	ICD 10 codes C22
Pancreas cancer	ICD 10 codes C25
Head & neck cancer	ICD 10 codes C00-C06, C09-C14 and C32
Kidney cancer	ICD 10 codes C64
Gallbladder cancer	ICD 10 codes C23
Esophagus cancer	ICD 10 codes C15

Abbreviations: ICD – International Classification of Disease

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Repeat visit	Variables	All (n=215,295)	Exercise frequency		cted by copyright, includin		
1 st			None (n=112,156)	1-2 times/week (n=57,777)		times/week	Almos everyo (n=13
	Sex, %	F4 40/	45.00/	04.00/		50.00/	40.00/
	Men Women	<u>51.1%</u> 48.9%	45.0% 55.0%	<u>61.8%</u> 38.2%	55.3% 55.3%	50.6%	<u>48.8%</u> 51.2%
	Age, years	52.7 (8.6)	53.6 (9.2)	50.9 (7.4)	44.7% eight 51.3 (7.5) eight e	523(80)	55.6 (9
	Body Mass Index, kg ² /m	23.5 (2.8)	23.4 (2.9)	23.6 (2.7)	23.7 (2.6)	23.6 (2.6)	23.7 (2
	Systolic blood pressure, mm Hg	120.5 (14.4)	120.6 (14.7)	120.4 (13.9)	120.0 (13. 6) 🗄 🖌	119.6 (13.9)	121.4
	Diastolic blood pressure, mm Hg	75.7 (9.9)	75.6 (9.9)	75.9 (9.8)	75.5 (9.8) 6 ഗ ≦	75.2 (9.8)	75.7 (9
	Fasting glucose levels, mg/dL	92.6 (18.5)	92.6 (18.8)	92.7 (17.4)	<u>92.4 (17.8) 주 등 등</u>	92.8 (21.0)	93.3 (2
	Total cholesterol, mg/dL	197.3 (36.2)	197.0 (36.8)	197.3 (35.6)	<u>197.9 (35. 🖺 🖣 🎽</u>	197.4 (35.9)	197.8
	Family history of heart disease, stroke or hypertension, %	12.6%	10.7%	14.2%	16.7% dieur dar	197.4 (35.9) 16.7%	12.0%
	Family history of cancer, %	14.3%	12.7%	15.5%	17.4% ឆៃ 🏹 o	19.2%	14.5%
	Family history of diabetes, %	6.0%	5.0%	6.7%		9.0%	5.8%
	Smoking status, % Never	70.7%	74.8%	62.4%		71.7%	74.8%
	Previously	8.6%	5.8%	11.9%	12.4%	11.9%	8.8%
	Currently	20.8%	19.4%	25.7%	18.7% 2		16.4%
-	Alcohol Consumption, %						
	Never	59.8%	66.9%	49.2%	52.7%		61.8%
	2-3 times/month	15.6%	12.7%	20.5%	18.6% ng	18.2%	12.8%
	1-2 times/week	15.8%	11.8%	21.7%	10.070	17.0%	14.8%
	≥3 times/week	8.8%	8.7%	8.6%	8.7% and s	10.0%	10.6%
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Repeat	Variables	All	3 rd , 4 th , 5 th and 6 Exercise		cted by copyright, includi	36/hmiopen-2018-025500	
visit 2 nd		(n=150,845)	frequency None (n=73,660)	1-2 times/week (n=44,211)	3-4 times/week (n=19,593	5-6 times/week	Almost everyday
	Sex, %				57.9% reigner 42.1% eigner 52.3 (7.4) ter	<u>(n=4,771)</u>	(n= 8,610
	Men	54.2%	47.0%	64.6%	57.9%	53.8%	53.5%
	Women	45.8%	53.0%	35.4%	42.1% 20	46.2%	46.5%
	Age, years	53.3 (8.3)	54.2 (8.9)	51.7 (7.2)	52.3 (7.4) * 6	53.4 (7.8)	56.5 (9.1)
	Body Mass Index, kg²/m	23.5 (2.7)	23.4 (2.8)	23.6 (2.6)	23.7 (2.6) - 2 .	23.6 (2.6)	23.6 (2.7)
	Systolic blood pressure, mm Hg	120.9 (14.1)	121.0 (14.5)	120.7 (13.7)	120.4 (13.6) 2		122.0 (14.
	Diastolic blood pressure, mm Hg	75.8 (9.6)	75.8 (9.7)	76.0 (9.5)	75.5 (9.4) e o	75.4 (9.4)	76.0 (9.8)
	Fasting glucose levels, mg/dL	93.2 (16.9)	93.1 (17.4)	93.5 (17.0)	93.1 (15.5) 4 5 197.8 (35. 2) 9	93.5 (15.9)	93.7 (16.2
	Total cholesterol, mg/dL	197.6 (35.9)	197.7 (36.5)	197.4 (35.4)	197.8 (35. Z) 4	196.7 (34.9)	198.1 (36.
	Family history of heart disease, stroke or hypertension, %	13.4%	11.2%	14.6%	17.5% d eid deid	18.3%	13.1%
	Family history of cancer, %	14.9%	12.9%	16.4%	17.4% a D	18.3% 19.7%	15.4%
	Family history of diabetes, %	6.3%	5.2%	7.1%	8.2% 3 2	9.0%	6.1%
	Smoking status, %	0.070	0.2,0			9.0% 71.2%	0.170
	Never	71.0%	76.5%	62.3%	68.7%	71.2%	74.2%
	Previously	9.0%	5.5%	12.5%	13.1%	13.1%	9.4%
	Currently	20.0%	18.0%	25.3%	18.2%	15.8%	16.5%
	Alcohol Consumption, %				Ω -	5	
	Never	59.0%	67.6%	48.1%		54.1%	60.0%
	2-3 times/month	16.1%	12.6%	20.9%	19.0% 5	18.9%	13.6%
	1-2 times/week	16.7%	12.1%	22.8%	20.7%	17.5%	15.8%
	≥3 times/week	8.1%	7.8%	8.2%	<u>a</u>	9.5%	10.7%
					ologie	om/ on lune 8 2025 at A	
						st Agence Riklingrankinge de l	

visit 3 rd		All (n=80,639)	Exercise frequency		ludii	36/bmiopen-2018-025590	
		(None (n= 36,123)	1-2 times/week (n=26,505)	3-4 times/week (n=11,432)	times/week	Almo ever (n=4
Se	ex, %				se	ar	
	Men	63.1%	53.9%	73.0%	68.6% ~ %	64.5%	63.4
	Women	36.9%	46.1%	27.0%	31.4% e.g 51.9 (6.6) e e	8 35.6%	36.7
Ac	ge, years	52.3 (7.2)	52.9 (7.8)	51.2 (6.2)	51.9 (6.6) ਨੂੰ ਰੱ	<u>52.8 (7.0)</u>	55.2
	bdy Mass Index, kg²/m	23.5 (2.7)	23.3 (2.8)	23.6 (2.6)	23.7 (2.5) C	-23.7(2.6)	23.7
	/stolic blood pressure, mm Hg	121.1 (13.6) 76.1 (9.4)	<u>120.9 (13.9)</u> 76.0 (9.5)	<u>120.9 (13.4)</u> 76.4 (9.4)	121.0 (13. 2)	5 120.0 (13.3) 5 75.6 (0.5)	122. 76.3
	asting glucose levels, mg/dL	93.7 (16.8)	93.3 (17.1)	94.1 (16.7)	76.1 (9.1) 6 0	<u>75.6 (9.5)</u>	94.5
	tal cholesterol, mg/dL	197.1 (35.2)	197.1 (35.5)	197.4 (34.8)	93.9 (15.9) 4 5 196.9 (34. 2) 9	1965(352)	196.
Fa	amily history of heart disease, stroke or pertension, %	13.5%	11.4%	14.8%	16.7% d. e.	18.6% 18.9%	11.7
	amily history of cancer, %	14.8%	13.0%	15.8%	17.8% ឆ 🕞	o 18.9%	14.7
	amily history of diabetes, %	6.4%	5.3%	7.0%	8.0% 3 🖫	9.5%	6.2%
Sr	noking status, %				nis		
	Never	66.6%	73.8%	57.6%	63.9% <u>6</u> .	65.5%	68.8
	Previously	10.7%	6.1%	14.0%	15.5%	16.6%	12.4
	Currently	22.8%	20.2%	28.4%		17.9%	18.7
Al	cohol Consumption, % Never	53.6%	64.2%	42.5%		47.4%	53.9
	2-3 times/month	18.5%	14.0%	23.7%	20.8% n	21.4%	15.8
	1-2 times/week	19.5%	14.0%	25.6 %	22.8%	20.7%	18.8
	≥3 times/week	8.4%	7.8%	8.3%	9.2%	10.5%	11.5
					ologie	om/ on June 8. 2025 at Agence Bibliographique d	

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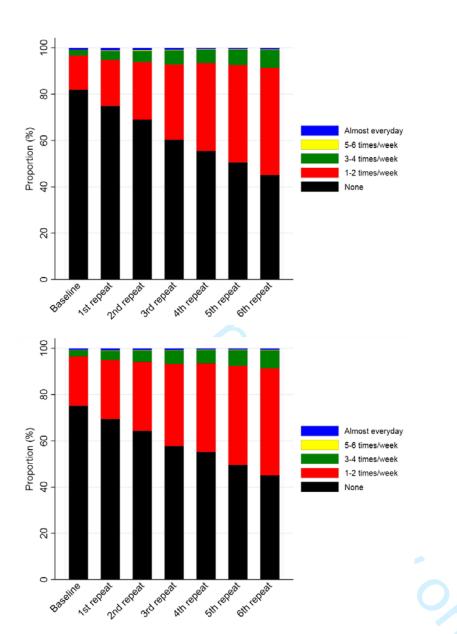
Repeat	Variables	All	Exercise		cted by copyright, includi	<u>7</u> 70	
visit 4 th		(n=40,910)	frequency None (n=17,678)	1-2 times/week (n=14,624)	3-4 times/week (n= 5,685)	5-6	Almost everyday (n=1,829)
	Sex, %				se		(11=1,029)
	Men	72.3%	61.6%	81.1%	81.5% 26	78.2%	73.9%
	Women	27.7%	38.4%	18.9%	18.5% e.g 50.7 (5.3) e e	21.9%	26.1%
	Age, years	50.9 (5.4)	51.2 (5.5)	50.6 (5.1)	<u>50.7 (5.3)</u>	51.0 (5.6)	52.6 (6.3)
	Body Mass Index, kg ² /m	23.5 (2.7)	23.3 (2.7)	23.7 (2.6)	23.8 (2.6)		23.7 (2.6)
	Systolic blood pressure, mm Hg	121.4 (13.3)	120.9 (13.5)	121.7 (13.0)	121.5 (12.8) ž		122.7 (13
	Diastolic blood pressure, mm Hg	76.6 (9.2) 93.9 (17.8)	76.2 (9.3) 93.3 (17.9)	77.0 (9.2) 94.4 (17.9)	76.8 (8.9) 6 0	76.8 (9.4)	77.2 (9.5) 94.9 (18.8
	Total cholesterol, mg/dL	196.8 (35.0)	197.2 (35.5)	196.7 (34.6)	94.3 (17.1) - 5 196.6 (34. 2) 9	1050 (3/3)	196.5 (34
	Family history of heart disease, stroke or	12.3%	10.4%	13.7%	14.2%	16.3%	11.6%
	hypertension, %	12.070	10.170	10.170	e = e	10.070	11.070
	Family history of cancer, %	13.8%	12.6%	14.7%	15.0% ឆី 🔁	16.3%	13.5%
	Family history of diabetes, %	5.7%	4.8%	6.2%	6.9% 3 🖫	7.5% 57.3%	6.7%
	Smoking status, %				n S		
	Never	60.6%	69.5%	51.9%	55.5%	57.3%	62.0%
	Previously	12.2%	6.9%	15.1%	18.7%	18.7%	15.7%
	Currently	27.2%	23.7%	33.0%		24.0%	22.4%
	Alcohol Consumption, %	10.404	00.00/	00.00/			45 40/
	Never	48.1%	60.0%	38.0%		39.9%	45.4%
	2-3 times/month	20.5% 22.4%	15.5% 16.2%	24.9%	24.3% D	24.0%	19.7%
	1-2 times/week ≥3 times/week	9.0%	8.2%	28.4% 8.7%	26.3% 9 10.3% n	22.6% 13.6%	22.9% 12.0%

$\begin{array}{c c c c c c c c c c c c c c c c c c c $	3-4 times/ (n=3,884) 82.4% 17.6% 51.0 (4.7) 23.8 (2.4) 121.6 (12. 76.8 (8.8) 94.7 (16.6) 196.4 (33. 14.3% 14.3% 54.4% 19.3% 26.2% 38.3%	2.4% 5 (4) 7.6% (4) 1.0 (4.7) 16 3.8 (2.4) d 21.6 (12.6) 5.8 (8.8) 6 4.7 (16.6 1 4.7 (16.6 1 4.3% d 4.3% d 4.9% f 4.9% f 4.3% f 4.9% f 4.3% f 4.9% f 4.3% f 4.9% f 4.3% f	nseignement Superieur (Авну 884)	on 13 March 201	times/week (n=724) 81.2%	Aln eve (n=
Men 73.7% 62.6% 81.6% 82.4 Women 26.3% 37.4% 18.4% 17.6 Age, years 51.1 (4.9) 51.4 (5.1) 50.8 (4.7) 51.0 Body Mass Index, kg ² /m 23.5 (2.6) 23.3 (2.7) 23.7 (2.6) 23.8 Systolic blood pressure, mm Hg 121.4 (13.0) 121.0 (13.4) 121.8 (12.9) 121. Diastolic blood pressure, mm Hg 76.6 (9.1) 76.2 (9.1) 77.1 (9.0) 76.8 Fasting glucose levels, mg/dL 94.3 (17.6) 93.7 (18.1) 94.6 (17.3) 94.7 Total cholesterol, mg/dL 197.1 (34.5) 197.7 (34.8) 196.7 (34.2) 196. Family history of heart disease, stroke or 12.6% 11.3% 13.4% 14.3 hypertension, % 14.3% 13.2% 15.1% 14.9 Family history of cancer, % 5.9% 4.9% 6.4% 6.79 Smoking status, % 5.9% 68.1% 50.8% 54.4 Previously 13.1% 7.1% 16.0% 19.3	82.4% 17.6% 51.0 (4.7) 23.8 (2.4) 121.6 (12. 76.8 (8.8) 94.7 (16.6) 196.4 (33. 14.3% 14.3% 14.9% 6.7% 54.4% 19.3% 26.2% 38.3%	See See 2.4% r 7.6% ela 1.0 (4.7) ela 3.8 (2.4) d 21.6 (12.6) ela 5.8 (8.8) ela 4.7 (16.64 ela 4.3% d 4.9% a 7% m 4.9% a 4.4% g 3.3% y	спseignement Superieur (АВс % (4.7) (2.4) б (12.6) text anin 6 (12.6) text anin (16.6) text anin % (16.6) text anin % (16.6) text anin % (16.6) text anin	arch 201 Enseigne	81.2%	(11-
Men 73.7% 62.6% 81.6% 82.4 Women 26.3% 37.4% 18.4% 17.6 Age, years 51.1 (4.9) 51.4 (5.1) 50.8 (4.7) 51.0 Body Mass Index, kg²/m 23.5 (2.6) 23.3 (2.7) 23.7 (2.6) 23.8 Systolic blood pressure, mm Hg 121.4 (13.0) 121.0 (13.4) 121.8 (12.9) 121. Diastolic blood pressure, mm Hg 76.6 (9.1) 76.2 (9.1) 77.1 (9.0) 76.8 Fasting glucose levels, mg/dL 94.3 (17.6) 93.7 (18.1) 94.6 (17.3) 94.7 Total cholesterol, mg/dL 197.1 (34.5) 197.7 (34.8) 196.7 (34.2) 196. Family history of heart disease, stroke or 12.6% 11.3% 13.4% 14.3 hypertension, % 14.3% 13.2% 15.1% 14.9 Family history of cancer, % 5.9% 4.9% 6.4% 6.79 Smoking status, % 5.9% 68.1% 50.8% 54.4 Previously 13.1% 7.1% 16.0% 19.3	82.4% 17.6% 51.0 (4.7) 23.8 (2.4) 121.6 (12.0 76.8 (8.8) 94.7 (16.6) 196.4 (33.0 14.3% 14.3% 14.9% 6.7% 54.4% 19.3% 26.2% 38.3%	2.4% 5 (4) 7.6% (4) 1.0 (4.7) 16 3.8 (2.4) d 21.6 (12.6) 5.8 (8.8) 6 4.7 (16.6 1 4.7 (16.6 1 4.3% d 4.3% d 4.9% f 4.9% f 4.3% f 4.9% f 4.3% f 4.9% f 4.3% f 4.9% f 4.3% f	899 grement Superieur (Авех (4.7) (2.4) (ch 201 seigne	81.2%	
Body Mass Index, kg²/m 23.5 (2.6) 23.3 (2.7) 23.7 (2.6) 23.8 Systolic blood pressure, mm Hg 121.4 (13.0) 121.0 (13.4) 121.8 (12.9) 121. Diastolic blood pressure, mm Hg 76.6 (9.1) 76.2 (9.1) 77.1 (9.0) 76.8 Fasting glucose levels, mg/dL 94.3 (17.6) 93.7 (18.1) 94.6 (17.3) 94.7 Total cholesterol, mg/dL 197.1 (34.5) 197.7 (34.8) 196.7 (34.2) 196.7 Family history of heart disease, stroke or hypertension, % 12.6% 11.3% 13.4% 14.3 Family history of diabetes, % 5.9% 4.9% 6.4% 6.79 Smoking status, % 5.9% 4.9% 6.4% 6.79 Mever 58.9% 68.1% 50.8% 54.4 Previously 13.1% 7.1% 16.0% 19.3 Currently 28.0% 24.8% 33.2% 26.2 Alcohol Consumption, % 7.1% 16.7% 25.8% 24.7 1-2 times/week 23.4% 17.4% 28.0% 27.3 <td>17.6% 51.0 (4.7) 23.8 (2.4) 121.6 (12.0 76.8 (8.8) 94.7 (16.6) 196.4 (33.0 14.3% 14.9% 6.7% 54.4% 19.3% 26.2% 38.3%</td> <td>7.6% e 1.0 (4.7) t 3.8 (2.4) d 21.6 (12.6) 5.8 (8.8) e 4.7 (16.6f 4.3% d 4.3% d</td> <td>% (4.7) elated (3.8) 6 (12.6) (8.8) (16.6) 4 (33.8) % % % % % %</td> <td>201</td> <td></td> <td>76.</td>	17.6% 51.0 (4.7) 23.8 (2.4) 121.6 (12.0 76.8 (8.8) 94.7 (16.6) 196.4 (33.0 14.3% 14.9% 6.7% 54.4% 19.3% 26.2% 38.3%	7.6% e 1.0 (4.7) t 3.8 (2.4) d 21.6 (12.6) 5.8 (8.8) e 4.7 (16.6 f 4.3% d 4.3% d	% (4.7) elated (3.8) 6 (12.6) (8.8) (16.6) 4 (33.8) % % % % % %	201		76.
Body Mass Index, kg²/m 23.5 (2.6) 23.3 (2.7) 23.7 (2.6) 23.8 Systolic blood pressure, mm Hg 121.4 (13.0) 121.0 (13.4) 121.8 (12.9) 121. Diastolic blood pressure, mm Hg 76.6 (9.1) 76.2 (9.1) 77.1 (9.0) 76.8 Fasting glucose levels, mg/dL 94.3 (17.6) 93.7 (18.1) 94.6 (17.3) 94.7 Total cholesterol, mg/dL 197.1 (34.5) 197.7 (34.8) 196.7 (34.2) 196.7 Family history of heart disease, stroke or hypertension, % 12.6% 11.3% 13.4% 14.3 Family history of diabetes, % 5.9% 4.9% 6.4% 6.79 Smoking status, % 5.9% 4.9% 6.4% 6.79 Mever 58.9% 68.1% 50.8% 54.4 Previously 13.1% 7.1% 16.0% 19.3 Currently 28.0% 24.8% 33.2% 26.2 Alcohol Consumption, % 7.1% 16.7% 25.8% 24.7 1-2 times/week 23.4% 17.4% 28.0% 27.3 <td>23.8 (2.4) 121.6 (12.6 76.8 (8.8) 94.7 (16.6) 196.4 (33.6 14.3% 14.9% 6.7% 54.4% 19.3% 26.2% 38.3%</td> <td>3.8 (2.4) d 21.6 (12.6) 5.8 (8.8) c 4.7 (16.6) 4.7 (16.6) 4.3% d 4.9% d</td> <td><u>(2.4)</u> <u>6</u> (12.6) (8.8) text (16.6) (16.</td> <td><u>16</u></td> <td>18.8%</td> <td>23.</td>	23.8 (2.4) 121.6 (12.6 76.8 (8.8) 94.7 (16.6) 196.4 (33.6 14.3% 14.9% 6.7% 54.4% 19.3% 26.2% 38.3%	3.8 (2.4) d 21.6 (12.6) 5.8 (8.8) c 4.7 (16.6) 4.7 (16.6) 4.3% d 4.9% d	<u>(2.4)</u> <u>6</u> (12.6) (8.8) text (16.6) (16.	<u>16</u>	18.8%	23.
Systolic blood pressure, mm Hg 121.4 (13.0) 121.0 (13.4) 121.8 (12.9) 121.4 Diastolic blood pressure, mm Hg 76.6 (9.1) 76.2 (9.1) 77.1 (9.0) 76.8 Fasting glucose levels, mg/dL 94.3 (17.6) 93.7 (18.1) 94.6 (17.3) 94.7 Total cholesterol, mg/dL 197.1 (34.5) 197.7 (34.8) 196.7 (34.2) 196. Family history of heart disease, stroke or hypertension, % 12.6% 11.3% 13.4% 14.3 Family history of cancer, % 14.3% 13.2% 15.1% 14.9 Family history of diabetes, % 5.9% 4.9% 6.4% 6.79 Smoking status, % 5.9% 68.1% 50.8% 54.4 Previously 13.1% 7.1% 16.0% 19.3 Currently 28.0% 24.8% 33.2% 26.2 Alcohol Consumption, % 46.3% 57.9% 37.6% 38.3 2-3 times/month 21.7% 16.7% 25.8% 24.7 1-2 times/week 23.4% 17.4% 28.0% 27.3	121.6 (12. 76.8 (8.8) 94.7 (16.6) 196.4 (33. 14.3% 14.9% 6.7% 54.4% 19.3% 26.2% 38.3%	21.6 (12.6) 5.8 (8.8) 4.7 (16.6) 96.4 (33.8) 4.3% 4.3% 4.9% 7% 7% 7% 1.1 min 9.3%	<u>6 (12.6)</u> (8.8) (16.6) (16.6) (16.6) (16.6) (16.6) (16.6) (16.6) (16.6) (16.6) (16.6) (16.6) (16.6) (12.6		51.4 (5.0)	52.
Diastolic blood pressure, mm Hg 76.6 (9.1) 76.2 (9.1) 77.1 (9.0) 76.8 Fasting glucose levels, mg/dL 94.3 (17.6) 93.7 (18.1) 94.6 (17.3) 94.7 Total cholesterol, mg/dL 197.1 (34.5) 197.7 (34.8) 196.7 (34.2) 196. Family history of heart disease, stroke or hypertension, % 12.6% 11.3% 13.4% 14.3 Family history of cancer, % 14.3% 13.2% 15.1% 14.9 Family history of diabetes, % 5.9% 4.9% 6.4% 6.79 Smoking status, % 5.9% 68.1% 50.8% 54.4 Previously 13.1% 7.1% 16.0% 19.3 Currently 28.0% 24.8% 33.2% 26.2 Alcohol Consumption, % 46.3% 57.9% 37.6% 38.3 2-3 times/month 21.7% 16.7% 25.8% 24.7 1-2 times/week 23.4% 17.4% 28.0% 27.3	76.8 (8.8) 94.7 (16.6) 196.4 (33. 14.3% 14.9% 6.7% 54.4% 19.3% 26.2% 38.3%	6.8 (8.8) te 4.7 (16.6 1 6.4 (33. 8 4.3% d 4.3% d 4.9% d 7% m n n 4.4% o 3.3%	(16.6) (1	ne L	23.7 (2.5)	23.
Fasting glucose levels, mg/dL 94.3 (17.6) 93.7 (18.1) 94.6 (17.3) 94.7 Total cholesterol, mg/dL 197.1 (34.5) 197.7 (34.8) 196.7 (34.2) 196. Family history of heart disease, stroke or hypertension, % 12.6% 11.3% 13.4% 14.3 Family history of cancer, % 14.3% 13.2% 15.1% 14.9 Family history of diabetes, % 5.9% 4.9% 6.4% 6.79 Smoking status, %	94.7 (16.6) 196.4 (33. 14.3% 14.9% 6.7% 54.4% 19.3% 26.2% 38.3%	4.7 (16.6) 96.4 (33.8) 4.3% 4.9% 4.9% 5.3% 4.9% 4.9% 4.9% 5.3%	(16.6) 4 (33.8) 6 data min 7 data min	₹ğ	120.8 (12.9)	12
Family history of heart disease, stroke or hypertension, % 12.6% 11.3% 13.4% 14.3 Family history of cancer, % 14.3% 13.2% 15.1% 14.9 Family history of diabetes, % 5.9% 4.9% 6.4% 6.79 Smoking status, % 5.9% 68.1% 50.8% 54.4 Previously 13.1% 7.1% 16.0% 19.3 Currently 28.0% 24.8% 33.2% 26.2 Alcohol Consumption, % 46.3% 57.9% 37.6% 38.3 2-3 times/month 21.7% 16.7% 25.8% 24.7 1-2 times/week 23.4% 17.4% 28.0% 27.3	14.3% 14.9% 6.7% 54.4% 19.3% 26.2% 38.3%	4.3% d 4.9% ta 7% min 4.4% ng 9.3% x	d data min	<u> 8</u>		76. 95.
Family history of heart disease, stroke or hypertension, % 12.6% 11.3% 13.4% 14.3 Family history of cancer, % 14.3% 13.2% 15.1% 14.9 Family history of diabetes, % 5.9% 4.9% 6.4% 6.79 Smoking status, % 5.9% 68.1% 50.8% 54.4 Previously 13.1% 7.1% 16.0% 19.3 Currently 28.0% 24.8% 33.2% 26.2 Alcohol Consumption, % 46.3% 57.9% 37.6% 38.3 2-3 times/month 21.7% 16.7% 25.8% 24.7 1-2 times/week 23.4% 17.4% 28.0% 27.3	14.3% 14.9% 6.7% 54.4% 19.3% 26.2% 38.3%	4.3% d 4.9% ta 7% min 4.4% ng 9.3% x	d data min		94.0(15.9)	95. 198
Family history of cancer, % 14.3% 13.2% 15.1% 14.9 Family history of diabetes, % 5.9% 4.9% 6.4% 6.7% Smoking status, % 58.9% 68.1% 50.8% 54.4 Previously 13.1% 7.1% 16.0% 19.3 Currently 28.0% 24.8% 33.2% 26.2 Alcohol Consumption, %	6.7% 54.4% 19.3% 26.2% 38.3%	7% mining 4.4% g.3%		rieur	13.8% 17.8%	10.
Smoking status, % Never 58.9% 68.1% 50.8% 54.4 Previously 13.1% 7.1% 16.0% 19.3 Currently 28.0% 24.8% 33.2% 26.2 Alcohol Consumption, %	6.7% 54.4% 19.3% 26.2% 38.3%	7% mining 4.4% g.3%		٥Ŀ	5 17.8%	13.
Never 58.9% 68.1% 50.8% 54.4 Previously 13.1% 7.1% 16.0% 19.3 Currently 28.0% 24.8% 33.2% 26.2 Alcohol Consumption, %	54.4% 19.3% 26.2% 38.3%	4.4% ng 9.3%	n ü	Έg	7.2%	8.6
Previously 13.1% 7.1% 16.0% 19.3 Currently 28.0% 24.8% 33.2% 26.2 Alcohol Consumption, %	19.3% 26.2% 38.3%	9.3%		S =		
Currently 28.0% 24.8% 33.2% 26.2 Alcohol Consumption, %	26.2% 38.3%		<u>%</u> <u>ng</u> .		57.0%	58.
Alcohol Consumption, % 57.9% 37.6% 38.3 2-3 times/month 21.7% 16.7% 25.8% 24.7 1-2 times/week 23.4% 17.4% 28.0% 27.3	38.3%	<u>5.2%</u>			19.8%	19.
Never 46.3% 57.9% 37.6% 38.3 2-3 times/month 21.7% 16.7% 25.8% 24.7 1-2 times/week 23.4% 17.4% 28.0% 27.3			<u>%</u>			21.
2-3 times/month 21.7% 16.7% 25.8% 24.7 1-2 times/week 23.4% 17.4% 28.0% 27.3			<u></u>		-	
1-2 times/week 23.4% 17.4% 28.0% 27.3	04 70/ 7					42.
				<u> </u>	22.2%	22.
≥3 times/week 8.6% 8.1% 2.5% 9.8%				<u> </u>	26.0% 10.5%	<u>25</u> . 9.7
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Repeat	Variables	All	Exercise		cted by copyright, includi	36/bmjopen-2018-025590	
visit 6 th		(n= 12,302)	frequency None (n= 4,684)	1-2 times/week (n=4,754)	3-4 times/%eek (n=1,929) o	S 5-6 ວີ times/week	Almost everyda
	Sex, %				USEN 84.7% SE	<u>ح (n=358)</u>	(n=577
	Men	76.2%	64.2%	83.8%	84.7% 5 6	R 80.7%	80.4%
	Women	23.8%	35.8%	16.2%	15.3%	≥ 19.3%	19.6%
	Age, years	51.3 (4.5)	51.6 (4.7)	51.0 (4.2)	15.3% eig 51.0 (4.4) t e	51.2 (4.3)	52.0 (5
	Body Mass Index, kg ² /m	23.6 (2.6)	23.3 (2.7)	23.7 (2.6)	23.8 (2.4) č. 3	23.6 (2.2)	23.7 (2
	Systolic blood pressure, mm Hg		121.2 (13.0)	121.6 (12.6)	121.7 (12. 6) ភ្	121.0 (12.5)	122.1 (
			76.4 (9.0)	77.0 (8.9)	77.0 (9.0) 6 0	<u>5 76.0 (8.7)</u>	76.3 (9
	Body Mass Index, kg²/m 23.6 (2.6) 23 Systolic blood pressure, mm Hg 121.5 (12.8) 12 Diastolic blood pressure, mm Hg 76.7 (9.0) 76 Fasting glucose levels, mg/dL 94.6 (18.5) 93 Total cholesterol, mg/dL 197.1 (34.5) 19 Family history of heart disease, stroke or hypertension, % 13.2% 11 Family history of cancer, % 14.5% 12 Family history of diabetes, % 6.4% 5 Smoking status, % 56.9% 66 Previously 14.0% 7 Currently 29.1% 26 Alcohol Consumption, % 24.8% 17	93.7 (18.8)	95.1 (18.7)	94.9 (16.6)	<u>95.1 (18.4)</u>	95.7 (2	
	Family history of heart disease, stroke or		<u>197.9 (35.0)</u> 11.7%	<u>197.1 (34.2)</u> 13.7%	15.5% 0 e 0 u	a 192.0 (32.2) 14.3% fo 15.1%	<u>197.4 (</u> 12.7%
	Family history of cancer, %	14.5%	12.9%	15.5%	15.7% a 🗘	1 5.1%	14.9%
			5.5%	6.4%	7.3% 3 B	3 7.3%	9.5%
					S in	<u>z</u>	
	Never		66.6%	48.7%	53.6%	57.3%	57.4%
			7.0%	17.3%	20.4%	16.8%	21.1%
		29.1%	26.5%	34.1%		26.0%	21.5%
		40 70/	FC F0/	25.00/	0	40 50/	07.00/
			56.5% 17.0%	35.0% 27.2%	36.4% n 24.9% n	40.5% 24.6%	37.8% 24.8%
			17.6%	30.0%	28.3%	24.0%	27.4%
			8.8%	7.9%	10.4%	8.4%	10.1%
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Supplementary Figure 1. Changes in proportions of exercise frequency categories across 7 time points in all 257,854 individuals who provided data at each respective assessment visit (top panel), and 12,302 individuals who provided data from all 7 assessment visits (bottom panel).

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Group Myocardial infarction Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday Stroke	HR (95% CI) 1.00 (1.00, 1.00) 0.98 (0.90, 1.07) 0.83 (0.73, 0.94) - 0.98 (0.79, 1.22) 0.97 (0.84, 1.12)	403356 220601 92749 22457) participants 148284 62923 24836 6676 15135	1741 723 276 88	40.6 31.7 29.2 38.2
Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	0.98 (0.90, 1.07) 0.83 (0.73, 0.94) - 0.98 (0.79, 1.22) 0.97 (0.84, 1.12)	220601 92749 22457	62923 24836 6676	723 276 88	31.7 29.2
Exercise frequency: 1-2 times/week	0.98 (0.90, 1.07) 0.83 (0.73, 0.94) - 0.98 (0.79, 1.22) 0.97 (0.84, 1.12)	220601 92749 22457	62923 24836 6676	723 276 88	31. 29.
Exercise frequency: 3-4 times/week	0.83 (0.73, 0.94) - 0.98 (0.79, 1.22) 0.97 (0.84, 1.12)	92749 22457	24836 6676	276 88	29.
Exercise frequency: 5-6 times/week	- 0.98 (0.79, 1.22) 0.97 (0.84, 1.12)	22457	6676	88	
Exercise frequency: Almost everyday	0.97 (0.84, 1.12)				
		40000	10100		46.
Stroke				219	40
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	9689	23
Exercise frequency: 1-2 times/week	0.86 (0.82, 0.89)	220601	62923	3333	14
Exercise frequency: 3-4 times/week	0.83 (0.79, 0.88)	92749	24836	1482	16
Exercise frequency: 5-6 times/week	0.80 (0.72, 0.88)	22457	6676	390	17
Exercise frequency: Almost everyday	0.95 (0.90, 1.01)	45038	15135	1240	27
Hypertension					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	65964	23
Exercise frequency: 1-2 times/week	0.98 (0.96, 0.99)	220601	62923	30623	21
Exercise frequency: 3-4 times/week	0.90 (0.89, 0.92)	92749	24836	12617	20
Exercise frequency: 5-6 times/week	0.91 (0.88, 0.94)	22457	6676	3294	21
Exercise frequency: Almost everyday	1.00 (0.97, 1.02)	45038	15135	7705	26
Type 2 diabetes					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	27128	14
Exercise frequency: 1-2 times/week	1.00 (0.98, 1.02)	220601	62923	13226	16
Exercise frequency: 3-4 times/week	0.91 (0.89, 0.94)		24836	5421	17
Exercise frequency: 5-6 times/week	0.92 (0.88, 0.97)		6676	1399	16
Exercise frequency: Almost everyday	1.01 (0.97, 1.04)	45038	15135	3285	17
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Group		HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	
Stomach cancer						
Exercise frequency: None (Reference)	•	1.00 (1.00, 1.00)	403356	148284	2672	
Exercise frequency: 1-2 times/week		1.01 (0.95, 1.09)	220601	62923	1160	
Exercise frequency: 3-4 times/week	_ →	0.94 (0.85, 1.03)	92749	24836	489	
Exercise frequency: 5-6 times/week		0.99 (0.83, 1.17)	22457	6676	139	
Exercise frequency: Almost everyday	→ +	0.93 (0.83, 1.04)	45038	15135	328	
Colon cancer						
Exercise frequency: None (Reference)	•	1.00 (1.00, 1.00)	403356	148284	1424	
Exercise frequency: 1-2 times/week		1.13 (1.03, 1.24)	220601	62923	692	
Exercise frequency: 3-4 times/week	→	1.12 (0.99, 1.27)	92749	24836	314	
Exercise frequency: 5-6 times/week		 1.20 (0.97, 1.48) 	22457	6676	90	
Exercise frequency: Almost everyday	-	1.02 (0.87, 1.18)	45038	15135	191	
Rectum cancer						
Exercise frequency: None (Reference)	•	1.00 (1.00, 1.00)	403356	148284	809	
Exercise frequency: 1-2 times/week	+	1.07 (0.94, 1.21)	220601	62923	378	
Exercise frequency: 3-4 times/week		0.95 (0.80, 1.13)	92749	24836	154	
Exercise frequency: 5-6 times/week	+	 1.07 (0.79, 1.43) 	22457	6676	46	
Exercise frequency: Almost everyday		1.01 (0.82, 1.23)	45038	15135	107	
Lung cancer			100		0.405	
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	2138	
Exercise frequency: 1-2 times/week	, 	0.97 (0.89, 1.05)	220601	62923	796	
Exercise frequency: 3-4 times/week		0.81 (0.72, 0.91)	92749	24836	307	
Exercise frequency: 5-6 times/week		0.80 (0.65, 1.00)	22457	6676	85	
Exercise frequency: Almost everyday		0.94 (0.83, 1.07)	45038	15135	275	
Liver cancer	I	4 00 /4 00 4 00	100050	44000	4.400	
Exercise frequency: None (Reference)	•	1.00 (1.00, 1.00)	403356	148284	1423	
Exercise frequency: 1-2 times/week	· +	1.07 (0.97, 1.17)	220601	62923	680	
Exercise frequency: 3-4 times/week		0.91 (0.80, 1.04)	92749	24836	263	
Exercise frequency: 5-6 times/week		0.99 (0.78, 1.24)	22457 45038	6676 15135	75 179	
Exercise frequency: Almost everyday		0.99 (0.84, 1.15)	45038	15135	179	
Pancreas cancer		4 00 (4 00 4 00)	100050	140004	400	
Exercise frequency: None (Reference)	_1.	1.00 (1.00, 1.00)	403356 220601	148284 62923	483 205	
Exercise frequency: 1-2 times/week		1.05 (0.89, 1.24)				
Exercise frequency: 3-4 times/week		 1.03 (0.82, 1.29) 0.08 (0.65, 1.48) 	92749	24836 6676	92 24	
Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		 0.98 (0.65, 1.48) 0.93 (0.71, 1.22) 	22457 45038	15135	24 60	
	· ·	0.00 (0.77, 1.22)	10000	10100		
Head&Neck cancer		1.00 (1.00, 1.00)	403356	148284	377	
Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week		1.00 (1.00, 1.00) 0.86 (0.71, 1.05)	220601	62923	144	
Exercise frequency: 3-4 times/week		0.96 (0.75, 1.24)	92749	24836	73	
Exercise frequency: 5-6 times/week		0.75 (0.44, 1.25)	22457	6676	15	
Exercise frequency: Almost everyday	· •	 0.96 (0.71, 1.29) 	45038	15135	47	
Kidney cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	301	
Exercise frequency: 1-2 times/week	_ _	➡ 1.10 (0.90, 1.34)	220601	62923	153	
Exercise frequency: 3-4 times/week		 1.20 (0.93, 1.54) 	92749	24836	75	
Exercise frequency: 5-6 times/week		 0.98 (0.59, 1.62) 	22457	6676	16	
Exercise frequency: Almost everyday		➡ 1.17 (0.85, 1.60)	45038	15135	44	
Gallbladder cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	219	
Exercise frequency: 1-2 times/week	•	0.97 (0.75, 1.25)	220601	62923	83	
Exercise frequency: 3-4 times/week		➡ 1.09 (0.79, 1.52)	92749	24836	43	
Exercise frequency: 5-6 times/week		➡ 1.48 (0.89, 2.45)	22457	6676	16	
Exercise frequency: Almost everyday		 1.32 (0.94, 1.86) 	45038	15135	39	
Esophagus cancer	Ţ	1.00 (1.00 . 1.00)	102250	148284	214	
Exercise frequency: None (Reference)	T	1.00 (1.00, 1.00)	403356 220601	148284 62923	214 75	
Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week		0.91 (0.70, 1.19)	92749	24836	75 29	
Exercise frequency: 5-6 times/week		0.76 (0.51, 1.12) 0.56 (0.25, 1.26)	22457	6676	29 6	
Exercise frequency: Almost everyday	•	→ 0.93 (0.62, 1.37) →	45038	15135	28	
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Supplementary Figure 2. Associations of exercise with incident myocardial infarction, stroke, hypertension and Type 2 diabetes (top panel) and various incident cancer outcomes (bottom panel). Note: Cox regression models using age as the underlying timescale were not adjusted for any confounders. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

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Group	HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Cruc rate
Myocardial infarction					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403105	148033	1526	35.6
Exercise frequency: 1-2 times/week	0.89 (0.81, 0.98)		62820	635	27.9
Exercise frequency: 3-4 times/week	0.82 (0.71, 0.94)		24802	246	26
Exercise frequency: 5-6 times/week	0.95 (0.75, 1.20)		6658	74	32.1
Exercise frequency: Almost everyday	0.95 (0.73, 1.20)		15111	197	41.8
	,,				
Stroke					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)		148033	9669	232.
Exercise frequency: 1-2 times/week	0.86 (0.82, 0.89)	220498	62820	3330	149
Exercise frequency: 3-4 times/week	0.83 (0.79, 0.88)	92715	24802	1481	160.
Exercise frequency: 5-6 times/week	0.80 (0.73, 0.89)	22439	6658	389	172.
Exercise frequency: Almost everyday	0.95 (0.90, 1.01)	45014	15111	1239	272
Hypertension					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403105	148033	65872	238
Exercise frequency: 1-2 times/week	0.92 (0.90, 0.93)	220498	62820	30585	211:
Exercise frequency: 3-4 times/week	0.86 (0.84, 0.88)		24802		2078
Exercise frequency: 5-6 times/week	0.87 (0.84, 0.90)		6658	3288	219
Exercise frequency: Almost everyday	0.95 (0.93, 0.97)		15111	7694	265
	0.33 (0.33, 0.37)	43014	13111	/034	205
Type 2 diabetes					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403105	148033	27101	1456
Exercise frequency: 1-2 times/week +	0.92 (0.90, 0.94)	220498	62820	13214	1669
Exercise frequency: 3-4 times/week	0.87 (0.84, 0.89)	92715	24802	5415	1743
Exercise frequency: 5-6 times/week	0.88 (0.84, 0.93)	22439	6658	1397	1679
Exercise frequency: Almost everyday	0.96 (0.93, 1.00)	45014	15111	3282	1736
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Group		HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	
Stomach cancer						_
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	2672	
Exercise frequency: 1-2 times/week	- -	0.90 (0.84, 0.97)	220601	62923	1160	
Exercise frequency: 3-4 times/week	<u> </u>	0.87 (0.79, 0.96)	92749	24836	489	
Exercise frequency: 5-6 times/week		0.93 (0.78, 1.10)	22457	6676	139	
Exercise frequency: Almost everyday		0.88 (0.78, 0.98)	45038	15135	328	
Exercise nequency. Annost everyddy	•	0.00 (0.70, 0.00)	40000	10100	520	
Colon cancer						
Exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	403356	148284	1424	
Exercise frequency: 1-2 times/week	+	1.05 (0.95, 1.15)	220601	62923	692	
Exercise frequency: 3-4 times/week	_ +	1.06 (0.93, 1.20)	92749	24836	314	
Exercise frequency: 5-6 times/week		→ 1.14 (0.92, 1.41)	22457	6676	90	
Exercise frequency: Almost everyday		0.97 (0.83, 1.12)	45038	15135	191	
Destrum senser						
Rectum cancer Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	809	
Exercise frequency: 1-2 times/week		0.96 (0.85, 1.09)	220601	62923	378	,
Exercise frequency: 3-4 times/week		0.88 (0.74, 1.05)	92749	24836	154	
Exercise frequency: 5-6 times/week		➡ 1.00 (0.74, 1.35)	22457	6676	46	-
Exercise frequency: Almost everyday		0.95 (0.78, 1.16)	45038	15135	107	1
Lung cancer						
Exercise frequency: None (Reference)	•	1.00 (1.00, 1.00)	403356	148284	2138	
Exercise frequency: 1-2 times/week		0.90 (0.83, 0.98)	220601	62923	796	
Exercise frequency: 3-4 times/week	→	0.80 (0.71, 0.91)	92749	24836	307	
Exercise frequency: 5-6 times/week	-	0.81 (0.65, 1.01)	22457	6676	85	
Exercise frequency: Almost everyday	-	0.93 (0.82, 1.05)	45038	15135	275	
Exercise inequency. / intest every aug	•	0.00 (0.02, 1.00)	40000	10100	210	
Liver cancer	1					
Exercise frequency: None (Reference)	. •	1.00 (1.00, 1.00)	403356	148284	1423	
Exercise frequency: 1-2 times/week	-+-	0.95 (0.87, 1.05)	220601	62923	680	
Exercise frequency: 3-4 times/week	→	0.85 (0.75, 0.98)	92749	24836	263	
Exercise frequency: 5-6 times/week		0.94 (0.74, 1.18)	22457	6676	75	
Exercise frequency: Almost everyday	-+ -	0.93 (0.79, 1.08)	45038	15135	179	
Pancreas cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	483	
Exercise frequency: 1-2 times/week	<u> </u>	1.02 (0.86, 1.20)	220601	62923	205	
		 1.02 (0.80, 1.20) 1.01 (0.81, 1.27) 	92749	24836	92	
Exercise frequency: 3-4 times/week						
Exercise frequency: 5-6 times/week		→ 0.97 (0.64, 1.46)	22457	6676	24	
Exercise frequency: Almost everyday		0.92 (0.70, 1.20)	45038	15135	60	
Head&Neck cancer						
Exercise frequency: None (Reference)	. ♦	1.00 (1.00, 1.00)	403356	148284	377	
Exercise frequency: 1-2 times/week	► I	0.76 (0.63, 0.93)	220601	62923	144	
Exercise frequency: 3-4 times/week		0.92 (0.71, 1.19)	92749	24836	73	
Exercise frequency: 5-6 times/week		0.73 (0.43, 1.22)	22457	6676	15	
Exercise frequency: Almost everyday	+	 0.92 (0.68, 1.25) 	45038	15135	47	
Kidney cancer						
Kidney cancer Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	301	
Exercise frequency: 1-2 times/week	• [0.95 (0.78, 1.17)	220601	62923	153	
Exercise frequency: 3-4 times/week		→ 1.10 (0.85, 1.42)	92749	24836	75	
Exercise frequency: 5-6 times/week		→ 0.93 (0.56, 1.54)	22457	6676	16	
Exercise frequency: 5-6 times/week	—	→ 1.11 (0.81, 1.52)	45038	15135	44	
		,				
Gallbladder cancer	1 I	1.00 (1.00, 4.00)	100050	140204	210	
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	219	
Exercise frequency: 1-2 times/week		 0.98 (0.75, 1.27) 	220601	62923	83	
Exercise frequency: 3-4 times/week		→ 1.09 (0.78, 1.52)	92749	24836	43	
Exercise frequency: 5-6 times/week		→ 1.47 (0.88, 2.45)	22457	6676	16	
Exercise frequency: Almost everyday		➡ 1.30 (0.93, 1.84)	45038	15135	39	
Esophagus cancer						
Exercise frequency: None (Reference)		1.00 (1.00, 1.00)	403356	148284	214	
Exercise frequency: 1-2 times/week		0.86 (0.65, 1.12)	220601	62923	75	
Exercise frequency: 3-4 times/week	← – –	0.78 (0.52, 1.15)	92749	24836	29	
Exercise frequency: 5-6 times/week		 0.57 (0.25, 1.29) 	22457	6676	6	
Exercise frequency: Almost everyday	-+	→ 0.90 (0.60, 1.33)	45038	15135	28	

Supplementary Figure 3. Associations of exercise with incident myocardial infarction, stroke, hypertension and Type 2 diabetes (top panel) and various incident cancer outcomes (bottom panel) after excluding data from the first 2-year follow-up period. Note: Cox regression models using age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of heart disease, stroke or hypertension (in models for incident myocardial infarction, stroke and hypertension), diabetes (in models for incident Type 2 diabetes) or cancer (in models for incident cancer outcomes), smoking status and alcohol consumption. Crude rates are per 100,000 person-years. "N"

indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. Abbreviations: HR - Hazard Ratio; CI - Confidence Intervals

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Page 39 of 49 1 2				BMJ C)pen		Body Mass Index ≥25 kg/	i 36/bmjopen-2018-025 cted by copyright,ජූාc				
3 4 5	Group	Body Mass Index <25 kg/	Iotal	Unique) participants(n) Events(n	Crude	Body Mass Index ≥25 kg/	8-0255 nt,ີ∰nct∰	Total	Unique I) participants	(n) Events(n	Crude) rate
6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42	Myocardial infarction Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/week Exercise frequency: Almost everyday Stroke Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 3-6 times/week Exercise frequency: 3-6 times/week Exercise frequency: 1-2 times/week Exercise frequency: 3-6 times/week Exercise frequency: 3-4 times/week Exercise frequency: 3-6 times/week Exercise frequency: 3-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 295683 0.94 (0.84, 1.04) 156729 0.75 (0.63, 0.88) 65633 ▶ 1.16 (0.91, 1.49) 16000 0.99 (0.84, 1.17) 31821 1.00 (1.00, 1.00) 295683 0.85 (0.81, 0.89) 156729 0.82 (0.77, 0.88) 65633 0.82 (0.77, 0.88) 65633 0.82 (0.77, 0.89) 156729 0.85 (0.83, 0.93) 16000 0.94 (0.87, 1.01) 31821 1.00 (1.00, 1.00) 295683 0.92 (0.91, 0.94) 156729 0.85 (0.83, 0.87) 65633 0.86 (0.82, 0.90) 16000 0.95 (0.92, 0.98) 31821 1.00 (1.00, 1.00) 295683 0.93 (0.90, 0.95) 156729 0.88 (0.85, 0.92) 65633 0.88 (0.82, 0.95) 16000 0.99 (0.95, 1.04) 31821 1.3	108755 44670 17543 4704 10658 108755 44670 17543 4704 10658 108755 44670 17543 4704 10658 108755	1181 487 163 66 150 8877 2227 990 272 842 44055 19638 7967 2079 4984 17229 7975 3291 844 2044	37.5 30 24.4 40.3 45 225.1 139.9 151.2 169.6 262.2 2061 1796.3 1745 1838.9 2296.9 613.2 552.4 548.3 575.7 697.4		90 org13 March 2019 ជាមួយពីទំនាំ២០៨៩៨ ទីថ្នាក់ដែលនៅទំនាំ២០ ទីក្លុងទីទីទៀពតិភូទីទាំងទី ឆ្នាំទីពេទីទេនី ទីទីទីទីទីទីទីទី iding3ថា ប្លទំនឹន relateds ទំនាំទីលេខាទីទី ទីទីទីទីទី ទំនាំទីទំនាំទី ក្រោយវិសាទ ទំនាំទី relateds ទំនាំទំនាំ និងទាំងទៅទំនាំទីទីទីទីទីទីទំនាំទីទំនាំទីទំនាំទីទំនាំទីទំនាំទីទំនាំទីទំនាំទំនាំ	1.00) 107673 0.90) 63872 1.07) 27116 1.04) 6457 1.11) 13217 1.00) 107673 0.96) 63872 0.95) 27116 0.94) 6457 1.10) 13217 1.00) 107673 0.95) 63872 0.94) 27116 0.98) 6457 1.02) 13217 1.00) 107673 0.95) 63872 0.91) 27116 0.98) 6457 1.01) 13217	18253 7293 1972 4477 39529 18253 7293 1972 4477 39529 18253 7293 1972 4477	560 236 113 22 69 2812 1106 492 118 398 21909 10985 4650 1215 2721 9899 5251 2130 555 1241	49 35.8 40.9 33 49.8 254.4 171.8 182 181.7 298.1 3474.6 3093.3 3098.2 3310.1 3709.4 1031.5 947.9 910.9 986.6 1069.5
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Group	Smoking: never	Total Unique HR (95% CI) cases(N) participant	Crude s(n) Events(n) rate	Smoking: pre	VIOUS Total Uniqu HR (95% CI) cases(N) particip		i 36/bmjopen-2018ஆ25590 on 13 cted by copyright ق گ	ent Total Unique HR (95% CI) cases(N) participa	c ints(n) Events(n) ra
Wyocardiai infarction Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 296255 106647 0.86 (0.76, 0.98) 130907 37173 0.73 (0.61, 0.88) 60735 16199 0.74 (0.53, 1.03) 15420 4553 0.99 (0.83, 1.18) 32380 10849	1011 32.3 333 24.8 137 22.3 37 23.5 139 41.2		1.00 (1.00, 1.00) 23702 8659 0.64 (0.48, 0.86) 28268 7571 0.72 (0.50, 1.03) 12863 3156 → 1.17 (0.71, 1.92) 3027 831 0.78 (0.49, 1.24) 4496 1337	132 52.1 75 25.7 40 30.5 18 58.2 21 44.5	590 on 13 luding fpr	1.00 (1.00, 1.00) 83399 32978 0.94 (0.81, 1.08) 61426 18179 0.89 (0.72, 1.10) 19151 5481 1.28 (0.90, 1.82) 4010 1252 0.87 (0.67, 1.14) 8162 2949	598 (315 4 99 4 33 7 59 (
Stroke Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 296255 106647 0.87 (0.83, 0.91) 130907 37173 0.84 (0.79, 0.90) 60735 16199 0.78 (0.69, 0.88) 15420 4593 0.95 (0.88, 1.01) 32380 10849	7174 236.7 2171 165.6 1050 175.3 271 176.5 909 280.4		1.00 (1.00, 1.00) 23702 8859 0.91 (0.79, 1.05) 28268 7571 0.77 (0.64, 0.93) 12863 3156 0.97 (0.74, 1.28) 3027 831 1.05 (0.85, 1.29) 4496 1337	507 205.3 363 126.4 148 114.8 56 184.8 112 245.4	Uses	1.00 (1.00, 1.00) 83399 32978 0.82 (0.75, 0.89) 61426 18179 0.85 (0.75, 0.96) 19151 5481 0.79 (0.61, 1.01) 4010 1252 0.92 (0.80, 1.06) 8162 2949	2008 799 284 63 219
Hypertension Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	+ + +	1.00 (1.00, 1.00) 296255 106647 0.89 (0.88, 0.91) 130907 37173 0.82 (0.81, 0.84) 60735 16199 0.86 (0.82, 0.89) 15420 4593 0.93 (0.90, 0.95) 32380 10849	47918 2346.4 17968 2035.9 8086 1979.9 2223 2110.5 5556 2625.7		1.00 (1.00, 1.00) 23702 8659 0.91 (0.87, 0.95) 28268 7571 0.88 (0.83, 0.93) 12863 3156 0.87 (0.79, 0.96) 3027 831 0.96 (0.88, 1.04) 4496 1337	4168 2733.5 3967 2282.3 1791 2339.4 446 2396.9 708 2629.5	sh 2019. Down seignementes related to te	1.00 (1.00, 1.00) 83399 32978 0.98 (0.95, 1.01) 61426 18179 0.97 (0.93, 1.01) 19151 5481 0.95 (0.88, 1.03) 4010 1252 1.03 (0.97, 1.09) 8162 2949	13878 8688 2740 625 1441
Type 2 diabetes Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	+ + 	1.00 (1.00, 1.00) 296255 106647 0.90 (0.88, 0.93) 130907 37173 0.86 (0.83, 0.89) 60735 16199 0.87 (0.81, 0.83) 15420 4593 0.97 (0.93, 1.01) 32380 10849	18858 677.3 7336 612.3 3377 614.8 889 633.9 2313 782.6		1.00 (1.00, 1.00) 23702 8659 0.90 (0.84, 0.97) 28268 7571 0.90 (0.83, 0.98) 12863 3156 0.87 (0.75, 1.01) 3027 831 0.98 (0.87, 1.11) 4496 1337	1691 776.7 1685 669.5 787 693.5 196 733 322 793	. Downloaded fro genttSuperidur (A d to text and data	1.00 (1.00, 1.00) 83399 32978 0.95 (0.91, 0.98) 61426 18179 0.87 (0.82, 0.93) 19151 5481 0.96 (0.85, 1.07) 4010 1252 0.95 (0.88, 1.03) 8162 2949	6579 4205 1257 314 650
					0.8 (0.7, 1.01) 3027 831 0.98 (0.87, 1.11) 4496 1337 1.3		m http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de I BES) . mining, Al training, and similar technologies.		
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Exercise frequency: 1-2 times/week 0.89 (0.78, 1.00) 101852 29973 Exercise frequency: 3-4 times/week 0.80 (0.88, 0.59, 45914 12548 Exercise frequency: Almost everyday 0.90 (0.76, 1.08) 26299 8971 Stroke 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 3-4 times/week 0.88 (0.83, 0.92) 101852 29973 Exercise frequency: 3-4 times/week 0.88 (0.83, 0.92) 101852 29973 Exercise frequency: 3-4 times/week 0.86 (0.80, 0.90) 11619 3489 Exercise frequency: 3-4 times/week 0.96 (0.89, 1.03) 26299 8971 Hypertension 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 3-4 times/week 0.96 (0.89, 1.03) 26299 8971 Exercise frequency: 1-2 times/week 0.90 (0.80, 0.90) 11619 3489 Exercise frequency: 3-4 times/week 0.90 (0.80, 0.91) 10522 29973 Exercise frequency: 3-4 times/week 0.90 (0.80, 0.92) 101852 29973 Exercise frequency: 4-100 (1.00, 1.00) 263051 95580 95580 Exercise frequency: 3-4 times/week 0.90 (0.80, 0.95) 101852 29973 Exercise frequency: 1-2 times/week 0.90 (0.80, 0.95) 101852 29973 Exercise frequency: 3-4 times/week 0.93 (0.90, 0.96) 26299 8971 Type 2 diabets 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 3-4 times/week </th <th>1164 41.9 364 34.8 150 32.4 47 39.8 134 48.9 6896 256.7 1890 185 880 194.9 227 197.2 2321 192.7 19227 192.2 1655 1964.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 706.6 1949 813.9 Crude (n) Events(n) rate 197 36</th> <th>e HR (95% Cl) cases(N) particip 9 1.00 (1.00, 1.00) 54349 20514 4 0.97 (0.72, 1.31) 18554 4897 5 0.74 (0.40, 1.36) 4333 1255 6.7 0.74 (0.40, 1.36) 4333 1255 7.2 0.74 (0.46, 1.19) 6456 2127 6.7 1.00 (1.00, 1.00) 54349 20514 5 0.76 (0.65, 0.89) 16854 4897 7.2 0.80 (0.61, 1.04) 4353 1255 2.7 0.80 (0.61, 1.04) 4353 1255 7.8 0.96 (0.82, 1.18) 6456 2127 6.5 0.98 (0.82, 1.18) 6456 2127 7.8 0.90 (0.81, 1.04) 4353 1255 7.7 0.98 (0.82, 1.18) 6456 2127 6.8 0.97 (0.87, 1.08) 6456 2127 9.9 0.82 (0.79, 0.91) 18554 4897 0.81 (0.84, 0.99, 0.88) 18554 4897 0.82 (0.72, 0.94) 4353 1255 1.00 (1.00, 1.00) 54349 20514 1.7 0.93 (0.88, 0.88) 64562 13400 0.82 (0.72, 0.94) 4353 1255 1.9 0.97 (0.87, 1.08) 6456 2127 1 1.3 1.3</th> <th>4 186 0 147 U 57 11 4 886 0 536 202 57 130 0 2649 1006 0 4 3210 0 2649 954 0 225 1006 0 225 295 1006 0 249 229 397</th>	1164 41.9 364 34.8 150 32.4 47 39.8 134 48.9 6896 256.7 1890 185 880 194.9 227 197.2 2321 192.7 19227 192.2 1655 1964.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 706.6 1949 813.9 Crude (n) Events(n) rate 197 36	e HR (95% Cl) cases(N) particip 9 1.00 (1.00, 1.00) 54349 20514 4 0.97 (0.72, 1.31) 18554 4897 5 0.74 (0.40, 1.36) 4333 1255 6.7 0.74 (0.40, 1.36) 4333 1255 7.2 0.74 (0.46, 1.19) 6456 2127 6.7 1.00 (1.00, 1.00) 54349 20514 5 0.76 (0.65, 0.89) 16854 4897 7.2 0.80 (0.61, 1.04) 4353 1255 2.7 0.80 (0.61, 1.04) 4353 1255 7.8 0.96 (0.82, 1.18) 6456 2127 6.5 0.98 (0.82, 1.18) 6456 2127 7.8 0.90 (0.81, 1.04) 4353 1255 7.7 0.98 (0.82, 1.18) 6456 2127 6.8 0.97 (0.87, 1.08) 6456 2127 9.9 0.82 (0.79, 0.91) 18554 4897 0.81 (0.84, 0.99, 0.88) 18554 4897 0.82 (0.72, 0.94) 4353 1255 1.00 (1.00, 1.00) 54349 20514 1.7 0.93 (0.88, 0.88) 64562 13400 0.82 (0.72, 0.94) 4353 1255 1.9 0.97 (0.87, 1.08) 6456 2127 1 1.3 1.3	4 186 0 147 U 57 11 4 886 0 536 202 57 130 0 2649 1006 0 4 3210 0 2649 954 0 225 1006 0 225 295 1006 0 249 229 397
Myocardial infarction Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: Almost everyday Stroke Exercise frequency: Almost everyday Stroke Exercise frequency: Almost everyday Stroke Exercise frequency: Almost everyday Control (1.00, 1.00) 263051 95580 0.88 (0.78, 0.89) 45914 12548 0.90 (0.76, 1.08) 26299 8971 1.00 (1.00, 1.00) 263051 95580 0.88 (0.78, 0.89) 45914 12548 0.88 (0.83, 0.82) 101852 29973 0.84 (0.78, 0.89) 45914 12548 0.78 (0.89, 0.911619 3489 0.86 (0.89, 1.03) 26299 8971 Hypertension Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: 5-6 times/week Exercise frequency: 5-6 times/week Exercise frequency: 5-6 times/week Exercise frequency: 1-2 times/week Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 4-100 (1.00, 1.00) 263051 95580 0.90 (0.80, 0.89) 11619 3489 0.90 (0.80, 0.89) 11619 3489 0.90 (0.80, 0.90) 26299 8971 Type 2 diabets Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/w	1164 41.9 364 34.8 150 32.4 47 39.8 134 48.9 6896 256.7 1890 185 880 194.9 227 197.2 2321 192.7 19227 192.2 1655 1964.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 706.6 1949 813.9 Crude (n) Events(n) rate 197 36	.9 .00 (1.00, 1.00) 54349 20514 .8 .9 .97 (0.72, 1.31) 18554 4897 .9 .97 (0.72, 1.31) 18554 4897 .9 .07 (0.04, 0.1.30) 54349 20514 .9 .07 (0.04, 0.1.30) 54349 20514 .9 .07 (0.04, 0.1.30) 54349 20514 .9 .07 (0.04, 0.1.30) 54349 20514 .9 .08 (0.73, 0.91) 48252 13400 .7 .080 (0.61, 1.04) 4353 1255 .098 (0.82, 1.18) 6456 2127 .100 (1.00, 1.00) 54349 20514 .9 .080 (0.61, 0.04) 54349 20514 .9 .91 (0.84, 0.99) 4353 1255 .91 (0.84, 0.99) 4353 1255 .93 .91 (0.84, 0.99) 4353 1255 .91 (0.84, 0.99) 4353 1255 .91 (0.84, 0.99) 4353 1255 .91 (0.84, 0.99) 4353 1255 .91 (0.84, 0.99) 4353 1255 .91 (0.84, 0.99) 4353 1255 .91 (0.84, 0.99) 4353 1255 .91 (0.84, 0.99) 4353 1255 .93 .93 (0.86, 0.98) 4856 2127	4 186 0 147 U 57 11 4 886 0 536 202 57 130 0 2649 1006 0 4 3210 0 2649 954 0 225 1006 0 225 295 1006 0 249 229 397
Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: -5.6 times/week 0.89 (0.76, 1.00) 263051 95580 Exercise frequency: -5.6 times/week 0.89 (0.76, 1.00) 263051 95580 Exercise frequency: -2.1 times/week 0.88 (0.83, 0.29) 101852 29973 Exercise frequency: -2.6 times/week 0.89 (0.76, 1.00) 263051 95580 Exercise frequency: -2.6 times/week 0.88 (0.83, 0.29) 101852 29973 Exercise frequency: -2.6 times/week 0.88 (0.83, 0.29) 101852 29973 Exercise frequency: -2.6 times/week 0.88 (0.83, 0.29) 101852 29973 Exercise frequency: -2.6 times/week 0.88 (0.83, 0.29) 101852 29973 Exercise frequency: -2.6 times/week 0.96 (0.89, 1.03) 26299 8971 Exercise frequency: -2.6 times/week 0.96 (0.89, 1.03) 26299 8971 Exercise frequency: -2.6 times/week 0.90 (0.80, 0.22) 101852 29973 Exercise frequency: -2.1 times/week + Exercise frequency: -2.6 times/week + Exercise frequency: -3.6 times/week + Exercise frequency: -3.6 times/week 0.92 (0.80, 0.95) 101852 29973 <tr< th=""><th>364 348 150 32.4 47 39.8 134 48.9 6896 256.7 1890 185 880 194.9 227 197.2 821 312.7 42572 2321.6 13905 1981.7 155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5033 636.5 2656 641.7 7743 7065 1949 813.9 Crude (n) Events(n) rate</th><th>.8. .9.9 (0.74, 1.15) 4252 13400 .9.9 .9.74 (0.40, 1.36) 4353 1255 .9.9 .74 (0.40, 1.36) 433 1255 .6.7 .0.07 (0.40, 1.30) 4333 1255 .7 .0.01 (0.00, 1.00) 54349 20514 .9.9 .74 (0.46, 1.19) 6456 2127 6.7 .0.07 (0.85, 0.89) 18554 4897 .72 .0.80 (0.81, 1.04) 4353 1255 2.7 .0.80 (0.81, 1.04) 4353 1255 .7 .0.80 (0.81, 1.04) 4353 1255 .7.7 .0.91 (0.84, 0.99) 4353 1255 .7.8 .0.91 (0.84, 0.99) 4353 1255 .7.7 .0.91 (0.84, 0.99) 4353 1255 .8.4 .0.92 (0.89, 0.96) 48522 13400 .7.7 .0.91 (0.84, 0.99) 4353 1255 .8.4 .0.91 (0.84, 0.99) 4353 1255 .9.9 .9.93 (0.88, 0.89) 48252 13400 .9.91 (0.84, 0.99) 4353 1255 .9.91 (0.84, 0.99) 4353 1255 .9.91 (0.84, 0.99) 4353 1255 .9.91 (0.84, 0.99) 4353 1255 .9.91 (0.84, 0.99) 4353 125</th><th>4 886 0 147 17 19 4 886 0 536 202 57 130 0 6205 2255 595 1006 2255 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 1007 1006 1007 1007 1007 100 1007 1007 100 100</th></tr<>	364 348 150 32.4 47 39.8 134 48.9 6896 256.7 1890 185 880 194.9 227 197.2 821 312.7 42572 2321.6 13905 1981.7 155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5033 636.5 2656 641.7 7743 7065 1949 813.9 Crude (n) Events(n) rate	.8. .9.9 (0.74, 1.15) 4252 13400 .9.9 .9.74 (0.40, 1.36) 4353 1255 .9.9 .74 (0.40, 1.36) 433 1255 .6.7 .0.07 (0.40, 1.30) 4333 1255 .7 .0.01 (0.00, 1.00) 54349 20514 .9.9 .74 (0.46, 1.19) 6456 2127 6.7 .0.07 (0.85, 0.89) 18554 4897 .72 .0.80 (0.81, 1.04) 4353 1255 2.7 .0.80 (0.81, 1.04) 4353 1255 .7 .0.80 (0.81, 1.04) 4353 1255 .7.7 .0.91 (0.84, 0.99) 4353 1255 .7.8 .0.91 (0.84, 0.99) 4353 1255 .7.7 .0.91 (0.84, 0.99) 4353 1255 .8.4 .0.92 (0.89, 0.96) 48522 13400 .7.7 .0.91 (0.84, 0.99) 4353 1255 .8.4 .0.91 (0.84, 0.99) 4353 1255 .9.9 .9.93 (0.88, 0.89) 48252 13400 .9.91 (0.84, 0.99) 4353 1255 .9.91 (0.84, 0.99) 4353 1255 .9.91 (0.84, 0.99) 4353 1255 .9.91 (0.84, 0.99) 4353 1255 .9.91 (0.84, 0.99) 4353 125	4 886 0 147 17 19 4 886 0 536 202 57 130 0 6205 2255 595 1006 2255 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 1007 1006 1007 1007 1007 100 1007 1007 100 100
Exercise frequency: 1-2 times/week 0.89 (0.79, 1.00) 101852 29973 Exercise frequency: 3-4 times/week 0.89 (0.79, 1.00) 101852 29973 Exercise frequency: Almost everyday 0.80 (0.80, 0.39) 45914 12548 Stroke 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 3-4 times/week 0.86 (0.83, 0.92) 101852 29973 Exercise frequency: 3-4 times/week 0.86 (0.83, 0.92) 101852 29973 Exercise frequency: 3-4 times/week 0.86 (0.83, 0.92) 101852 29973 Exercise frequency: 3-4 times/week 0.86 (0.83, 0.92) 101852 29973 Exercise frequency: 3-4 times/week 0.86 (0.80, 0.30) 26299 8971 Hypertension 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 3-4 times/week + Exercise frequency: 1-2 times/week + Exercise frequency: 3-4 times/week + Exercise frequency: 3-4 times/week + Exercise frequency: 1-2 times/week +	364 348 150 32.4 47 39.8 134 48.9 6896 256.7 1890 185 880 194.9 227 197.2 821 312.7 42572 2321.6 13905 1981.7 155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5033 636.5 2656 641.7 7743 7065 1949 813.9 Crude (n) Events(n) rate	.8. .9.9 (0.74, 1.15) 4252 13400 .9.9 .9.74 (0.40, 1.36) 4353 1255 .9.9 .74 (0.40, 1.36) 433 1255 .6.7 .0.07 (0.40, 1.30) 4333 1255 .7 .0.01 (0.00, 1.00) 54349 20514 .9.9 .74 (0.46, 1.19) 6456 2127 6.7 .0.07 (0.85, 0.89) 18554 4897 .72 .0.80 (0.81, 1.04) 4353 1255 2.7 .0.80 (0.81, 1.04) 4353 1255 .7 .0.80 (0.81, 1.04) 4353 1255 .7.7 .0.91 (0.84, 0.99) 4353 1255 .7.8 .0.91 (0.84, 0.99) 4353 1255 .7.7 .0.91 (0.84, 0.99) 4353 1255 .8.4 .0.92 (0.89, 0.96) 48522 13400 .7.7 .0.91 (0.84, 0.99) 4353 1255 .8.4 .0.91 (0.84, 0.99) 4353 1255 .9.9 .9.93 (0.88, 0.89) 48252 13400 .9.91 (0.84, 0.99) 4353 1255 .9.91 (0.84, 0.99) 4353 1255 .9.91 (0.84, 0.99) 4353 1255 .9.91 (0.84, 0.99) 4353 1255 .9.91 (0.84, 0.99) 4353 125	4 886 0 536 202 57 130 4 8003 0 6205 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595
Exercise frequency: 3-4 times/week 0.80 (0.86, 0.95) 45914 12548 Exercise frequency: Almost everyday 0.90 (0.76, 1.02) 1199 3489 Stroke 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: Almost everyday 0.96 (0.81, 0.22) 195580 Exercise frequency: Almost everyday 0.96 (0.81, 0.22) 10152 29973 Stroke 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: Almost everyday 0.96 (0.81, 0.30) 1119 3489 Exercise frequency: Almost everyday 0.96 (0.81, 0.30) 1119 3489 Exercise frequency: Almost everyday 0.96 (0.81, 0.30) 1119 3489 Exercise frequency: S-6 times/week 0.90 (0.80, 0.20) 11522 29973 Exercise frequency: S-6 times/week 0.90 (0.80, 0.20) 11652 29973 Exercise frequency: S-6 times/week 0.90 (0.80, 0.90) 11619 3489 Exercise frequency: S-6 times/week 0.90 (0.80, 0.911652 29973 Exercise frequency: Almost everyday + 0.92 (0.89, 0.95) 11652 29973 Type 2 diabetes 1.00 (1.00, 1.00) 263051 95580	150 32.4 47 39.8 134 48.9 6896 256.7 1890 185 980 194.9 227 197.2 821 312.7 42572 2321.6 13905 1961.7 42572 2321.6 13055 1964.7 155 1954.5 1644 2031.8 4593 636.5 2656 641.7 743 7043 1949 813.9 Crude (n) Events(n) rate 197 36	.4	4 886 0 536 202 57 130 4 8003 0 6205 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595 1006 2253 595
Exercise frequency: Almost everyday 0.90 (0.76, 1.08) 26299 8971 Stroke 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 3-4 times/week 0.88 (0.83, 0.82) (01652 29973 Exercise frequency: 5-6 times/week 0.86 (0.83, 0.82) (01552 29973 Exercise frequency: Almost everyday 0.96 (0.90, 0.90) (1619 3489 Phypertension 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 3-4 times/week + 0.96 (0.89, 0.90) (16192 29973 Exercise frequency: 1-2 times/week + 0.96 (0.80, 0.22) (01552 29973 Exercise frequency: 3-4 times/week + 0.90 (0.80, 0.22) (01552 29973 Exercise frequency: 3-4 times/week + 0.84 (0.81, 0.80, 0.45) 1452 29973 Exercise frequency: 3-4 times/week + 0.80 (0.81, 0.100) 263051 95580 Exercise frequency: 1-2 times/week + 0.92 (0.89, 0.35) 101552 29973 Exercise frequency: 1-2 times/week + 0.80 (0.81, 0.1100) 263051 95580 Exercise frequency: 3-4 times/week + 0.83 (0.80, 0.11652 29973 Exercise frequency: 1-2 times/week + 0.80 (0.80, 0.11652 29973<	134 48.9 6896 256.7 1890 185 880 194.9 227 197.2 821 312.7 42572 2321.6 1305 1961.7 155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 706.8 1949 813.9 Crude (n) Events(n) rate 197 36	.9 6.7 5 4.9 7.2 2.7 2.1.6 6.7 5. 4.9 7.2 2.7 2.1.6 6.7 5. 4.9 7.2 2.7 2.7 4.9 4.9 5. 5. 5. 4.9 7.2 2.7 4.9 4.9 5. 5. 7.2 2.7 4.9 5. 5. 5. 5. 7. 2.7 4.9 5. 5. 5. 5. 5. 5. 5. 5. 5. 5.	19 4 8866 0 536 202 57 130 4 8003 4 8003 0 6205 2253 595 1006 4 3210 0 2649 954 229 397
Stroke 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 1-2 times/week 0.88 (0.83, 0.22) 101552 29973 Exercise frequency: 5-6 times/week 0.84 (0.78, 0.90) 45914 12548 Exercise frequency: 1-2 times/week 0.86 (0.8, 0.22) 101552 29973 Exercise frequency: 3-4 times/week 0.86 (0.8, 0.22) 101552 29973 Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 1-2 times/week 0.90 (0.88, 0.92) 101552 29973 Exercise frequency: 3-4 times/week 0.90 (0.88, 0.92) 101552 29973 Exercise frequency: Almost everyday + Type 2 diabets 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 3-4 times/week + Exercise frequency: 3-6 times/week + Exercise frequency: 3-6 times/week +	6896 256.7 1890 185 880 194.9 227 197.2 821 312.7 42572 2321.6 13905 1961.7 6155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 706.6 1949 813.9 Crude (n) Events(n) rate 197 36	6.7 5 4.9 7.2 2.7 21.6 6.7 5.7 2.7 21.6 6.7 5.7 2.7 21.6 6.7 5.7 2.7 21.6 6.7 5.7 2.7 21.6 6.7 5.7 2.7 21.6 6.7 5.7 2.7 2.7 2.7 2.7 2.7 2.7 2.7 2	4 886 4 202 57 130 6 4 8003 6 225 5 1006 9 4 3210 0 24 3210 0 954 9 1006 9 1006 9 1006 9 1006 9 1006 9 1006 9 1007 9 1
Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 5-6 times/week Exercise frequency: 5-6 times/week Exercise frequency: 1-2 times/week Exercise frequency: 1-2 times/week Exercise frequency: 1-2 times/week Exercise frequency: A ti	1890 185 980 194,9 227 197.2 821 312.7 42572 2321.6 13905 1961.7 6155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 706.6 1949 813.9 Crude (n) Events(n) / rate 197 36	5 4.9 7.2 2.7 21.6 61.7 5.5 4.9 7.7 2.7 21.6 61.7 5.5 4.9 7.7 2.7 21.6 61.7 54.5 75.7 1.00 (1.00, 1.00) 54349 0.80 (0.81, 1.04) 48552 1.3400 0.81 (0.43, 0.83) 1255 1.00 (1.00, 1.00) 54349 0.84 (0.80, 0.88) 18554 1.09 (0.84, 0.99) 4353 1.255 1.01 (0.85, 1.98) 6456 2.127 0.91 (0.84, 0.99) 4353 1.255 1.01 (0.85, 1.98) 6456 2.127 0.81 (0.79, 0.91) 1.9554 4897 0.82 (0.72, 0.94) 4353 1.255 0.97 (0.87, 1.08) 6456 2.127 1.3 Alcohol consumption: ≥3times/week Unique	4 886 4 0 536 - 202 57 130 4 4 8003 6 2255 5 1006 9 4 3210 0 4 3210 0 249 954 9 229 397 3 397 3 397 3 229 10 397 3 397 3 307 307 3 307 3 307 307 3 307 3 307 307 30
Exercise frequency: 1-2 times/week + 0.88 (0.83, 0.22) (1052 29973 Exercise frequency: 3-4 times/week 0.88 (0.83, 0.22) (1052 29973 0.84 (0.78, 0.90) 45914 12548 Exercise frequency: Almost everyday + 0.88 (0.83, 0.22) (1052 29973 0.84 (0.78, 0.90) 45914 12548 Hypertension 1.00 (1.00, 1.00) 263051 95580 0.90 (0.88, 0.22) (101852 29973 0.84 (0.81, 0.88) 45914 12548 Exercise frequency: 3-4 times/week + 0.90 (0.88, 0.22) (101852 29973 0.90 (0.88, 0.22) (101852 29973 Exercise frequency: Almost everyday + 0.90 (0.80, 0.26) (101852 29973 0.90 (0.80, 0.88) (101119 3489 Exercise frequency: Almost everyday + 0.93 (0.90, 0.96) 26299 8971 0.93 (0.90, 0.96) 26299 8971 Type 2 diabetes 1.00 (1.00, 1.00) 263051 95580 1.00 (1.00, 1.00) 263051 95580 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 3-4 times/week + 0.93 (0.87, 1.01) 11619 3489 0.98 (0.84, 0.91) 45914 12548 Exercise frequency: 3-4 times/week + 0.98 (0.84, 0.91) 45914 12548 0.98 (0.84, 0.91) 45914 12548 Corrup - - 0.98 (0.94, 0.95) 101852 29973 0.98 (0.94, 0.91) 45914 12548 . - 0.98 (0.94, 0.91) 4552 195780 0.98 (0.94, 0.91) 45914 12548 <td< td=""><td>1890 185 980 194,9 227 197.2 821 312.7 42572 2321.6 13905 1961.7 6155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 706.6 1949 813.9 Crude (n) Events(n) / rate 197 36</td><td>5 4.9 7.2 2.7 21.6 61.7 5.5 4.9 7.7 2.7 21.6 61.7 5.5 4.9 7.7 2.7 21.6 61.7 54.5 75.7 1.00 (1.00, 1.00) 54349 0.80 (0.81, 1.04) 48552 1.3400 0.81 (0.43, 0.83) 1255 1.00 (1.00, 1.00) 54349 0.84 (0.80, 0.88) 18554 1.09 (0.84, 0.99) 4353 1.255 1.01 (0.85, 1.98) 6456 2.127 0.91 (0.84, 0.99) 4353 1.255 1.01 (0.85, 1.98) 6456 2.127 0.81 (0.79, 0.91) 1.9554 4897 0.82 (0.72, 0.94) 4353 1.255 0.97 (0.87, 1.08) 6456 2.127 1.3 Alcohol consumption: ≥3times/week Unique</td><td>0 536 202 5 57 130 2 4 8003 6 0 6205 5 595 5 1006 5 4 3210 6 954 954 954 954 954 954 957 997</td></td<>	1890 185 980 194,9 227 197.2 821 312.7 42572 2321.6 13905 1961.7 6155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 706.6 1949 813.9 Crude (n) Events(n) / rate 197 36	5 4.9 7.2 2.7 21.6 61.7 5.5 4.9 7.7 2.7 21.6 61.7 5.5 4.9 7.7 2.7 21.6 61.7 54.5 75.7 1.00 (1.00, 1.00) 54349 0.80 (0.81, 1.04) 48552 1.3400 0.81 (0.43, 0.83) 1255 1.00 (1.00, 1.00) 54349 0.84 (0.80, 0.88) 18554 1.09 (0.84, 0.99) 4353 1.255 1.01 (0.85, 1.98) 6456 2.127 0.91 (0.84, 0.99) 4353 1.255 1.01 (0.85, 1.98) 6456 2.127 0.81 (0.79, 0.91) 1.9554 4897 0.82 (0.72, 0.94) 4353 1.255 0.97 (0.87, 1.08) 6456 2.127 1.3 Alcohol consumption: ≥3times/week Unique	0 536 202 5 57 130 2 4 8003 6 0 6205 5 595 5 1006 5 4 3210 6 954 954 954 954 954 954 957 997
Exercise frequency: 3-4 times/week 0.84 (0.78, 0.90) 45914 12548 0.78 (0.69, 0.90) 11619 3489 0.78 (0.69, 0.90) 11619 3489 0.78 (0.69, 0.90) 11619 3489 0.96 (0.89, 1.03) 26299 8971 Hypertension Exercise frequency: None (Reference) Exercise frequency: 5-6 times/week Exercise frequency: 5-6 times/week Exercise frequency: 1-2 times/week Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/week Exercise frequency: 1-2 times/week 0.92 (0.89, 0.95) 101852 29973 0.88 (0.84, 0.91 45914 12548 0.92 (0.89, 0.95) 101852 29973 0.88 (0.84, 0.91 45914 12548 0.93 (0.80, 0.9145914 12548 0.93 (0.80, 0.9145914 12548 0.93 (0.87, 1.01) 11619 3489 0.98 (0.84, 0.91 45914 12548 0.93 (0.87, 1.01) 11619 3489 0.98 (0.84, 0.914 5914 12548	880 194.9 227 197.2 821 312.7 42572 2321.6 13905 1961.7 1955 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5033 636.5 1949 813.9 Crude (n) Events(n) rate 197 36	4.9 7.2 2.7 7.2 2.7 7.2 2.7 7.2 2.7 7.2 2.7 7.2 2.7 7.2 2.7 7.2 2.7 7.2 2.7 7.2 2.7 7.2 2.7 7.5 7.5 7.5 7.5 7.5 7.5 7.5 7	202 57 130 4 8003 2253 595 1006 4 3210 0 2649 954 229 397
Exercise frequency: Almost everyday 0.96 (0.89, 1.03) 26299 8971 Hypertension 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: None (Reference) 1.00 (0.80, 0.22) 101852 29973 Exercise frequency: 3-4 times/week 0.84 (0.81, 0.86) 45914 12548 Exercise frequency: Almost everyday 0.83 (0.90, 0.86) 26299 8971 Type 2 diabetes 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 1-2 times/week 0.92 (0.89, 0.95) f01552 29973 Exercise frequency: 2-4 times/week 0.92 (0.80, 0.96) 10552 29973 Exercise frequency: 3-4 times/week 0.92 (0.80, 0.96) 10552 29973 Exercise frequency: Almost everyday 0.92 (0.80, 0.96) 10552 29973 .3 1 1.3 1.3 Corpus HR (95% CI) cases(N) participants(n) Myocardial infarction 1.00 (1.00, 1.00) 51117 18407 Exercise frequency: 3-4 times/week 0.88 (0.40, 0.94) 19850 5027 Exercise frequency:	821 312.7 42572 2321.6 13905 1961.7 6155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 706.6 1949 813.9 Crude (n) Events(n) rate	2.7 0.98 (0.82, 1.18) 6456 2127 21.6 1.7 1.00 (1.00, 1.00) 54349 20514 61.7 0.92 (0.89, 0.86) 48252 13400 0.84 (0.80, 0.88) 18554 4897 0.91 (0.84, 0.99) 4353 1255 1.01 (0.95, 1.08) 6456 2127 8.4 0.93 (0.88, 0.98) 48252 13400 0.84 (0.80, 0.88) 18554 4897 0.91 (0.84, 0.99) 4353 1255 1.01 (0.95, 1.08) 6456 2127 0.85 (0.79, 0.91) 18554 4897 0.82 (0.72, 0.94) 4353 1255 3.9 0.82 (0.72, 0.94) 4353 1255 0.97 (0.87, 1.08) 6456 2127 1 1.3 Alcohol consumption: ≥3times/week Ude	4 8003 2253 595 1006 4 3210 0 2649 954 229 397
Hypertension 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 1-2 times/week 0.90 (0.80, 0.22) 101852 29973 Exercise frequency: 3-4 times/week 0.84 (0.81, 0.84) 45914 12548 Exercise frequency: Almost everyday + Type 2 diabetes 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: Almost everyday + Type 2 diabetes 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: Almost everyday + Type 2 diabetes 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 1-2 times/week + Exercise frequency: 3-4 times/week + Exercise frequency: Almost everyday + 0.98 (0.84, 0.91 45914 12548 12548 Exercise frequency: Almost everyday 0.98 (0.84, 0.91 45914 12548 Exercise frequency: Almost everyday 0.98 (0.94, 1.03) 26299 8971 1 .3 1.3 Altochol consumption: 1-2times/week 0.98 (0.94, 1.03) 26299 8971 Image: Consumption: 1-2times/week 0.98 (0.94, 1.03) 26299 8971 Image: Consumption: 1-2times/week 0.98 (0.94, 1.03) 26299 8971 Image: Consumption: 1-2times/week 0.88 (0.40, 0.94) 19815 132548 Exercise frequency: None (Reference)	42572 2321.6 13905 1981.7 6155 1984.7 6155 1984.7 1684 2031.8 4507 2575.7 17226 698.4 5933 636.5 2856 641.7 7743 706.6 1949 813.9 Crude (n) Events(n) rate	21.6 1.00 (1.00, 1.00) 54349 20514 61.7 0.92 (0.89, 0.89) 48252 13400 75.7 0.84 (0.80, 0.88) 18554 4897 8.4 0.91 (0.84, 0.99) 4353 1255 1.00 (1.00, 1.00) 54349 20514 0.91 (0.84, 0.99) 4353 1255 1.00 (1.00, 1.00) 54349 20514 0.93 (0.88, 0.89) 48252 13400 0.85 (0.79, 0.91) 18554 4897 0.82 (0.72, 0.94) 4353 1255 0.97 (0.87, 1.08) 6456 2127 1 1.3	4 8003 2253 595 1006 4 3210 0 2649 954 229 397
Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 3-4 times/week + Exercise frequency: 5-6 times/week + Exercise frequency: 3-4 times/week + Exercise frequency: 1-2 times/week + Exercise frequency: 3-4 times/week + Exercise frequency: 1-2 times/week + Exercise frequency: 3-4 times/week + Exercise frequency: 1-2 times/week + Exercise frequency: 3-4 times/week + Exercise frequency: 1-2 times/week + Exercise frequency: 3-4 times/week + 0.98 (0.94, 0.91) 45914 12548 2548 0.93 (0.90, 0.96) 26299 8971 0.98 (0.94, 0.91) 45914 12548 Exercise frequency: 3-4 times/week + 0.98 (0.94, 0.91) 45914 12548 0.98 (0.94, 0.91) 45914 12548 0.93 (0.90, 0.96) 26299 8971 0.98 (0.94, 0.91) 45914 12548 0.93 (0.90, 0.96) 26299 8971 0.98 (0.94, 0.91) 45914 12548 0.93 (0.97, 1.01) 11615 3489 0.98 (0.94, 0.94) 19850 5027	13905 1961.7 6155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 7068 1949 813.9 Crude (n) Events(n) rate 197 36	61.7 54.5 57.7 6.6 6.5 7.7 6.6 6.5 7.7 6.6 6.5 7.7 6.6 6.5 7.7 6.6 7.7 6.6 7.7 6.6 7.7 6.6 7.7 7.7	4 8003 0 6205 595 1006 4 3210 0 2649 954 229 397
Exercise frequency: 1-2 times/week + 0.90 (0.88, 0.92) 101652 29973 Exercise frequency: 3-4 times/week + 0.84 (0.81, 0.89) 101652 29973 Exercise frequency: Almost everyday + 0.84 (0.81, 0.89) 101652 29973 Type 2 diabetes 0.93 (0.90, 0.96) 26299 8971 Exercise frequency: Almost everyday + 0.92 (0.89, 0.95) 101852 29973 Type 2 diabetes 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 3-4 times/week + Exercise frequency: 4-4 times/week + Exercise frequency: 3-4 times/week + Exercise frequency: Almost everyday + .3 1 .3 1 .3 1 .3 1 .3 1 .3 1 .4 0.87 (0.70, 1.08) 51538 13815 .5 0.87 (0.70, 1.08) 51538 13815 .5 0.88 (0.49, 0.49) 19850 5027 Exercise frequency: 3-4 times/week - .5 0.88 (0.49, 0.49) 1	13905 1961.7 6155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 7068 1949 813.9 Crude (n) Events(n) rate 197 36	61.7 54.5 57.7 6.6 6.5 7.7 6.6 6.5 7.7 6.6 6.5 7.7 6.6 6.5 7.7 6.6 7.7 6.6 7.7 6.6 7.7 6.6 7.7 7.7	0 6205 595 1006 4 3210 0 2649 954 229 397
Exercise frequency: 3-4 times/week + 0.84 (0.81, 0.86) 45914 12548 Exercise frequency: 3-6 times/week + 0.84 (0.80, 0.88) 11619 3489 Exercise frequency: Almost everyday + 0.83 (0.80, 0.88) 11619 3489 Type 2 diabetes 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 1-2 times/week + 0.88 (0.84, 0.91) 45914 12548 Exercise frequency: 1-2 times/week + 0.88 (0.84, 0.91) 45914 12548 Exercise frequency: 3-4 times/week + 0.88 (0.84, 0.91) 45914 12548 Exercise frequency: 3-4 times/week + 0.88 (0.84, 0.91) 45914 12548 Exercise frequency: Almost everyday + 0.98 (0.94, 1.03) 26299 8971 1 .3 1 1.3 Altochol consumption: 1-2times/week Exercise frequency: None (Reference) Total Unique Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 51117 18407 Osroup HR (95% CI) cases(N) participants(n) 0.88 (0.49, 0.94) 19850 5027 Exercise frequency: 3-4 times/week - 0.78 (0.70, 1.09) 51538 13815 0.78 (0.70, 1.09) 5138 <td>6155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 706.6 1949 813.9 Crude (n) Events(n) rate</td> <td>54.5 31.8 75.7 6.4 6.5 1.7 6.6 3.9 Classified and a state of the state of</td> <td>1006 4 3210 0 2649 954 229 397 397</td>	6155 1954.5 1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 743 706.6 1949 813.9 Crude (n) Events(n) rate	54.5 31.8 75.7 6.4 6.5 1.7 6.6 3.9 Classified and a state of the state of	1006 4 3210 0 2649 954 229 397 397
Exercise frequency: -56 times/week	1644 2031.8 4507 2575.7 17226 698.4 5933 636.5 2656 641.7 7743 7066 1949 813.9 Crude (n) Events(n) rate	31.8 0.91 (0.84, 0.99) 4353 1255 75.7 1.01 (0.05, 1.08) 6456 2127 8.4 0.93 (0.88, 0.99) 4252 13400 6.5 0.93 (0.88, 0.99) 4252 13400 1.7 0.85 (0.79, 0.91) 18554 4897 0.82 (0.72, 0.94) 4353 1255 0.97 (0.87, 1.08) 6456 2127 1 1.3 Allcohol consumption: ≥3times/week	1006 4 3210 0 2649 954 229 397 397
Type 2 diabetes 1.00 (1.00, 1.00) 263051 95580 Exercise frequency: 1-2 times/week 0.92 (0.89, 0.95) 101652 29973 Exercise frequency: 3-4 times/week 0.88 (0.84, 0.91) 45914 12548 Exercise frequency: Almost everyday 0.98 (0.94, 1.03) 26299 8971 Image: State Sta	17226 698.4 5933 636.5 2656 641.7 743 706.6 1949 813.9 Crude (n) Events(n) rate	8.4 6.5 1.7 6.6 3.9 Alcohol consumption: ≥3times/week Total Unique Total Unique Total Unique	4 3210 0 2649 954 229 397
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Exercise frequency: 1-2 times/week	5933 636.5 2656 641.7 743 7066 1949 813.9 Crude (n) Events(n) rate	6.5 1.7 6.6 3.9 Alcohol consumption: ≥3times/week ude	0 2649 954 229 397
Exercise frequency: 3-6 times/week • 0.88 (0.84, 0.91) 45914 12548 0.93 (0.87, 1.01) 11619 3489 0.98 (0.94, 1.03) 26299 8971 .3 1 1.3 .3 1 1.3 Group HR (95% CI) case(N) participants(n) Wyocardial Infarction Exercise frequency: None (Reference) Exercise frequency: 3-4 times/week 0.87 (0.70, 1.08) 51538 13815 0.88 (0.94, 0.94) 19950 5027	2656 641.7 743 706.6 1949 813.9 Crude (n) Events(n) rate	1.7 0.85 (0.79, 0.91) 18554 4897 6.6 0.82 (0.72, 0.94) 4353 1255 0.97 (0.87, 1.08) 6456 2127 1 1.3 Alcohol consumption: ≥3times/week Total Unique	954 229 397
Exercise frequency: 5-6 times/week 0.93 (0.87, 1.01) 11619 3489 Exercise frequency: Almost everyday 0.98 (0.94, 1.03) 26299 8971 .3 1 1.3 Alicohol consumption: 1-2times/week Group HR (95% CI) Total Unique Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 51117 18407 Exercise frequency: 3-4 times/week 0.87 (0.70, 1.08) 51538 13815 Exercise frequency: 3-4 times/week 0.78 (0.42, 1.43) 4161 1209	743 706,6 1949 813,9 Crude (n) Events(n) rate	6.6 0.82 (0.72, 0.94) 4353 1255 3.9 0.97 (0.87, 1.08) 6456 2127 1 1.3 Alcohol consumption: ≥3times/week Total Unique	229 397
Image: Second	Crude (n) Events(n) rate 197 36	Alcohol consumption: ≥3times/week	ې ز
Alcohol consumption: 1-2times/week	(n) Events(n) rate	Alcohol consumption: ≥3times/week	ې ز
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Myocardial infarction 1.00 (1.00, 1.00) 51117 18407 Exercise frequency: None (Reference) 0.87 (0.70, 1.08) 51538 13815 Exercise frequency: 3-4 times/week 0.88 (0.49, 0.94) 19850 5027 Exercise frequency: 5-6 times/week 0.78 (0.42, 1.43) 4161 1209	197 36	e HR (95% CI) cases(N) partici	le e
Exercise frequency: None (Reference) 1.00 (1.00, 1.00) 51117 18407 Exercise frequency: 1-2 times/week 0.87 (0.70, 1.00) 5153 13815 Exercise frequency: 3-4 times/week 0.68 (0.49, 0.94) 19850 5027 Exercise frequency: 5-6 times/week 0.78 (0.42, 1.43) 4161 1209			ipants(n) Events
Exercise frequency: 1-2 times/week 0.87 (0.70, 1.08) 51538 13815 Exercise frequency: 3-4 times/week 0.88 (0.49, 0.94) 19850 5027 Exercise frequency: 3-6 times/week 0.78 (0.42, 1.43) 4161 1209			<u>u</u>
Exercise frequency: 3-4 times/week 0.68 (0.49, 0.94) 19850 5027 Exercise frequency: 5-6 times/week 0.78 (0.42, 1.43) 4161 1209	152 28.5		60
	45 22	0.64 (0.42, 0.98) 8431 2364	24
Exercise inequency. Airlost everyday	11 25.4 33 43.6		19 33
	55 45.0		33
Stroke			
	902 168.3 574 109.2		222
Exercise frequency: 3-4 times/week	246 122.4		154
	58 136.7		48
Exercise frequency: Almost everyday 0.86 (0.72, 1.04) 7213 2200	132 179	9 0.94 (0.79, 1.11) 5070 1837	157
Hypertension			
	8339 2487.2		
	7151 2291.1 2782 2313.3		1427
Exercise frequency: 5-6 times/week - 0.91 (0.84, 0.99) 4161 1209	609 2331.8	31.8 0.93 (0.85, 1.03) 2324 723	446
Exercise frequency: Almost everyday 0.96 (0.91, 1.03) 7213 2200	1174 2691.4	91.4 0.99 (0.92, 1.05) 5070 1837	1018
Type 2 diabetes			
	3526 748.6		
	3185 693 1181 664.8	3 0.89 (0.84, 0.95) 18959 5735	
Exercise frequency: 5-6 times/week		(,,	630
Exercise frequency: Almost everyday 0.93 (0.84, 1.02) 7213 2200	244 647.3	4.8 ••• 0.85 (0.78, 0.93) 8431 2364	630 183
		4.8	183
	244 647.3	4.8	183

	No family history	of CVD					Family history of CVD				, I
Group		HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Crude rate		HR (95% CI)	Total cases(N)	Unique participants(n)	Events Copyright, Incarding
yocardial infarction											à
exercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	359412	132298	1576	41.2	+	1.00 (1.00, 1.00)	43944	15986	165
xercise frequency: 1-2 times/week	—	0.87 (0.79, 0.96)	189298	54170	621	31.7		0.84 (0.66, 1.09)	31303	8753	102
xercise frequency: 3-4 times/week xercise frequency: 5-6 times/week		0.81 (0.70, 0.93) 1.04 (0.83, 1.31)	77584 18631	20894 5573	237 78	29.9 40.7		0.70 (0.49, 0.99) 0.67 (0.35, 1.27)	15165 3826	3942 1103	39 P
xercise frequency: Almost everyday		0.93 (0.80, 1.09)	39732	13481	195	46.8	· · · · · · · · · · · · · · · · · · ·	 1.00 (0.65, 1.54) 	5306	1654	24 0
oke											es
kercise frequency: None (Reference)	4	1.00 (1.00, 1.00)	359412	132298	8756	236	4	1.00 (1.00, 1.00)	43944	15986	933
xercise frequency: 1-2 times/week	→	0.86 (0.82, 0.90)	189298	54170	2817	146.4		0.87 (0.78, 0.97)	31303	8753	516
xercise frequency: 3-4 times/week	→	0.82 (0.77, 0.87)	77584	20894	1212	156.1		0.89 (0.77, 1.02)	15165	3942	516 CC
xercise frequency: 5-6 times/week	→	0.82 (0.73, 0.91)	18631	5573	328	174.9		0.76 (0.59, 0.98)	3826	1103	
Exercise frequency: Almost everyday		0.96 (0.90, 1.02)	39732	13481	1109	275.9		0.91 (0.76, 1.10)	5306	1654	131
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xercise frequency: None (Reference)	+	1.00 (1.00, 1.00)	359412	132298	58611	2366.4	+	1.00 (1.00, 1.00)	43944	15986	7353
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29	Supplementary Figure 4. Resu	Its from runn	ing Cox regr	ession	model	s ex	amining	effect modification	n of sex,	body ma	iss inc	lex,	
30	smoking, alcohol consumption,		• •				•						rdial
31		•	•						<u> </u>			•	iaiai
32	infarction, stroke, hypertension				0				0 '	0			

adjusted for sex [not in models for effect modification by sex], body mass index [not in models for effect production by body mass index], systolic blood pressure, fasting glucose levels, total cholesterol levels, family history [not in mode fig for effect modification by family history of respective disease] of heart disease/stroke/hypertension (in models for myocardial infarctions stroke and hypertension), or diabetes (in models for Type 2 diabetes), smoking status [not in models for effect modification by smoking status] and alcohol consumption [not in models for effect modification by alcohol consumption]. Crude rates are per 2100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated a generate observations) and "n" indicates numbers of unique participants at baseline. P-values for multiplicative terms – myocardial afarction (p-value = 0.235), stroke (p-value = 0.363), hypertension (p-value = 0.050) and type 2 diabetes (p-value = 0.196) by body mass index;

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cted by copyright, Body Mass Index <25 kg/m² Body Mass Index ≥25 kg/m² includin Total cases(N) Unique participants(n) Crude rate Total cases(N) Unique participants(n) Group HR (95% CI) Events(n) HR (95% CI) Events(Stomach cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week 108755 44670 17543 4704 2005 802 343 89 235 1.00 (1.00, 1.00) 0.88 (0.81, 0.96) 0.87 (0.78, 0.98) 295683 156729 65633 64 49.6 1.00 (1.00, 1.00) 107673 39529 667 **Q**8.5 0.95 (0.83, 1.09) 0.87 (0.72, 1.04) 1.16 (0.87, 1.55) 63872 27116 6457 13217 358 146 50 93 54.4 075.3 67.2 18253 7293 1972 51.5 54.4 70.9 0.84 (0.68, 1.04) 0.87 (0.76, 0.99) 16000 31821 Exercise frequency: Almost everyday 10658 0.91 (0.73, 1.13) 4477 uses Colon cancel Joion cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 5-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday 1.00 (1.00, 1.00) 1.06 (0.94, 1.18) 1.12 (0.96, 1.29) 1.07 (0.82, 1.40) 0.93 (0.77, 1.12) 295683 156729 65633 16000 31821 108755 44670 17543 4704 10658 1019 471 224 58 127 32.4 1.00 (1.00, 1.00) 1.02 (0.86, 1.21) 0.93 (0.74, 1.17) 107673 63872 27116 39529 18253 7293 1972 4477 405 221 90 32 64 33.5 35.4 38.1 1.29 (0.90, 1.85) 6457 13217 1.05 (0.81, 1.37) Rectum cancer 108755 44670 17543 4704 10658 591 248 104 27 70 1.00 (1.00, 1.00) 1.09 (0.87, 1.37) 0.93 (0.68, 1.27) 1.37 (0.86, 2.20) 1.13 (0.79, 1.60) 107673 63872 27116 6457 13217 Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week 1.00 (1.00, 1.00) 0.91 (0.78, 1.06) 295683 156729 18.7 15.3 15.5 16.4 39529 18253 7293 1972 4477 218 130 50 19 37 Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday 0.87 (0.71 1.08) 65633 0.85 (0.58, 1.25) 16000 31821 0.89 (0.69, 1.14) 21 Lung cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-6 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday 1.00 (1.00, 1.00) 0.89 (0.81, 0.98) 0.76 (0.66, 0.87) 108755 44670 17543 4704 10658 295683 156729 65633 1708 605 220 61 198 54.4 37.3 430 191 87 24 77 1 00 (1 00 1 00) 107673 39520 1.00 (1.00, 1.00) 0.90 (0.75, 1.07) 0.92 (0.73, 1.16) 0.95 (0.63, 1.43) 107673 63872 27116 6457 13217 39529 18253 7293 1972 4477 32.9 37.2 59.6 0.76 (0.59, 0.99) 0.85 (0.73, 0.98) 16000 31821 1.17 (0.92, 1.49) Liver cancer Jver cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 5-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday 1.00 (1.00, 1.00) 0.99 (0.89, 1.11) 0.89 (0.76, 1.05) 1.07 (0.82, 1.40) 0.97 (0.81, 1.17) 295683 108755 1019 32.3 39529 18253 7293 1972 4477 404 210 84 18 51 1.00 (1.00, 1.00) 0.88 (0.74, 1.05) 107673 295683 156729 65633 16000 31821 108755 44670 17543 4704 10658 470 179 57 128 29 63872 27116 6457 13217 26.8 34.8 38.4 0.80 (0.63, 1.02) 0.69 (0.43, 1.10) 0.86 (0.64, 1.15) Pancreas cancer 373 142 68 20 45 Exercise frequency; 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Alcohol	consumption	1: never HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Crude rate	Alcohol consu	Imption: 2-3tin	Total cases(N)	onth
cy: None (Reference) cy: 1-2 timos/weak cy: 3-4 timos/weak cy: 5-6 timos/weak cy: 4-imos/weak cy: Almost everyday	+	1.00 (1.00, 1.00) 0.88 (0.80, 0.98) 0.93 (0.82, 1.07) 0.92 (0.72, 1.17) 0.84 (0.72, 0.98)	263051 101852 45914 11619 26299	95580 29973 12548 3489 8971	1650 521 258 69 177	59.5 49.9 55.9 58.5 64.9		1.00 (1.00, 1.00) 1.01 (0.85, 1.20) 0.72 (0.55, 0.94) 0.97 (0.64, 1.48) 0.90 (0.64, 1.27)	54349 48252 18554 4353 6456	20514 13400 4897 1255 2127
cy: None (Reference) cy: 1-2 times/week cy: 3-4 times/week cy: 5-6 times/week cy: Almost everyday	- +	1.00 (1.00, 1.00) 0.99 (0.87, 1.13) 1.00 (0.84, 1.19) 1.10 (0.82, 1.48) 1.01 (0.84, 1.23)	263051 101852 45914 11619 26299	95580 29973 12548 3489 8971	929 321 155 46 117	33.4 30.6 33.4 38.9 42.7		1.00 (1.00, 1.00) 1.09 (0.85, 1.39) 1.19 (0.87, 1.64) 1.56 (0.96, 2.53) 0.80 (0.48, 1.32)	54349 48252 18554 4353 6456	20514 13400 4897 1255 2127
cy: None (Reference) cy: 1-2 times/week cy: 3-4 times/week cy: 5-8 times/week cy: 5-8 times/week cy: Almost everyday	≕	1.00 (1.00, 1.00) 0.87 (0.73, 1.05) 0.79 (0.62, 1.02) 0.89 (0.57, 1.38) 0.80 (0.60, 1.07)	263051 101852 45914 11619 26299	95580 29973 12546 3489 8971	517 159 69 21 52	18.5 15.1 14.9 17.7 18.9	-	1.00 (1.00, 1.00) 0.99 (0.72, 1.38) 0.94 (0.60, 1.47) 1.37 (0.71, 2.64) 1.60 (0.98, 2.62)	54349 48252 18554 4353 6456	20514 13400 4897 1255 2127
cy: None (Reference) cy: 1-2 timos/week cy: 3-4 timos/week cy: 5-6 timos/week cy: Almost everyday		1.00 (1.00, 1.00) 0.96 (0.86, 1.08) 0.79 (0.67, 0.93) 0.87 (0.65, 1.16) 0.86 (0.73, 1.02)	283051 101852 45914 11619 28299	95580 29973 12548 3489 8971	1328 412 156 47 149	47.8 39.3 33.6 39.7 54.5		1.00 (1.00, 1.00) 0.85 (0.68, 1.07) 0.81 (0.58, 1.13) 0.75 (0.41, 1.38) 1.34 (0.94, 1.91)	54349 48252 18554 4353 6456	20514 13400 4897 1255 2127
cy: None (Reference) cy: 1-2 times/weak cy: 3-4 times/weak cy: 5-6 times/weak cy: 5-6 times/weak cy: Almost everyday		1.00 (1.00, 1.00) 0.95 (0.83, 1.08) 0.85 (0.70, 1.02) 1.05 (0.77, 1.42) 0.99 (0.81, 1.21)	263051 101852 45914 11619 26299	95580 29973 12548 3489 8971	873 314 130 43 110	31.4 30 28 36.3 40.1		1.00 (1.00, 1.00) 0.96 (0.76, 1.21) 0.64 (0.44, 0.93) 0.96 (0.54, 1.69) 0.46 (0.24, 0.88)	54349 48252 18554 4353 6456	20514 13400 4897 1255 2127

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Ē	zvercise frequency: 5-6 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	·	0.54 (0.13, 2)		3489 8971	29	1.7 3.3	·	=	0.36 (0.08, 1.56) 1.51 (0.34, 6.61) 0.81 (0.19, 3.54)	4353 6456	1255 2127	222	4.4 2.9	n g	, <mark>f</mark>
	Alcohol	consumptio	n: 1-2times	Total	Unique 4) participants(i	n) Events(n)	Crude rate	Alcohol consu	impt	i <mark>on:≥3tim</mark> ⊮R (95% CI)	es/we		Events(n)	Crude rate	 	/bmj
	omach cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: Altimos/week Exercise frequency: Altimost everyday	-==	1.00 (1.00, 1) 0.87 (0.74, 1) 0.79 (0.63, 1) 0.80 (0.51, 1) 0.99 (0.74, 1)	03) 51538 00) 19850 24) 4161	18407 13815 5027 1209 2200	335 254 92 21 55	61.4 47.7 45.2 48.7 73	⊒		1.00 (1.00, 1.00) 0.89 (0.73, 1.08) 0.95 (0.74, 1.23) 1.06 (0.71, 1.59) 0.89 (0.67, 1.17)	34839 18959 8431 2324 5070	13783 5735 2364 723 1837	409 141 71 25 59	110.2 71.6 82.2 104.4 110.6	raini	jopen
	lon cancer Exercise frequency: 1+2 times/week Exercise frequency: 1+2 times/week Exercise frequency: 3-4 times/week Exercise frequency: Altmost everyday	-	1.00 (1.00, 1) 1.01 (0.81, 1) 0.94 (0.70, 1) 1.18 (0.72, 1) 0.85 (0.56, 1)	26) 51538 26) 19850 94) 4161	18407 13815 5027 1209 2200	183 155 59 17 27	33.4 29 28.9 39.4 35.6	•		1.00 (1.00, 1.00) 1.36 (1.05, 1.78) 1.42 (1.01, 1.98) 0.78 (0.39, 1.60) 1.05 (0.71, 1.55)	34839 18959 8431 2324 5070	13783 5735 2364 723 1837	171 90 45 8 30	45.6 45.5 51.8 33.2 55.8	ng, a	.bmj.
	otum cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 timos/week Exercise frequency: 3-4 timos/week Exercise frequency: Altmost everyday	_	1.00 (1.00, 1) 1.14 (0.86, 1) 1.05 (0.71, 1) 1.29 (0.67, 2) 1.59 (1.03, 2)	52) 51538 54) 19850 48) 4161	18407 13815 5027 1209 2200	101 100 36 10 26	18.4 18.7 17.6 23.2 34.3			1.00 (1.00, 1.00) 1.15 (0.82, 1.63) 1.12 (0.71, 1.77) 0.78 (0.32, 1.91) 0.51 (0.28, 1.00)	34839 18959 8431 2324 5070	13783 5735 2354 723 1837	109 50 23 5 9	29 25.2 26.4 20.7 16.7	nd si	.com
	ng cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: Altimos/week Exercise frequency: Altimost everyday		1.00 (1.00, 1) 0.81 (0.67, 0) 0.78 (0.59, 1) 0.58 (0.31, 1) 0.72 (0.50, 1)	99) 51538 03) 19850 05) 4161	18407 13815 5027 1209 2200	283 169 63 11 32	51.8 31.6 30.9 25.4 42.3	<u> </u>		1.00 (1.00, 1.00) 0.86 (0.68, 1.10) 0.87 (0.63, 1.19) 0.97 (0.59, 1.61) 1.10 (0.83, 1.45)	34839 18959 8431 2324 5070	13783 5735 2384 723 1837	329 90 43 16 57	88.2 45.5 49.5 66.3 106.6		on
	er cancer Ixercise frequency: None (Reference) Zercise frequency: 1-2 timos/week Zercise frequency: 3-4 timos/week Zercise frequency: 6-8 timos/week Exercise frequency: Almost everyday		1.00 (1.00, 1) 0.90 (0.72, 1) 0.85 (0.70, 1) 0.86 (0.48, 1) 0.78 (0.50, 1)	12) 51538 27) 19850 54) 4161	18407 13815 5027 1209 2200	187 147 60 12 23	34.1 27.5 29.4 27.8 30.4	·		1.00 (1.00, 1.00) 1.02 (0.78, 1.32) 1.03 (0.72, 1.46) 0.60 (0.28, 1.27) 1.16 (0.81, 1.66)	34839 18959 8431 2324 5070	13783 5735 2364 723 1837	203 81 38 7 36	54.2 40.9 43.7 28.9 67.2	r tec	June
	ncreas cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 timos/week Exercise frequency: 3-4 timos/week Exercise frequency: Altmost everyday		1.00 (1.00, 1) 1.23 (0.78, 1) 1.55 (0.90, 2) 1.28 (0.46, 3) 0.13 (0.02, 0)	96) 51538 69) 19850 59) 4161	18407 13815 5027 1209 2200	41 37 20 4 1	7.5 6.9 9.8 9.2 1.3			1.00 (1.00, 1.00) 1.01 (0.60, 1.72) 0.87 (0.41, 1.85) 2.06 (0.88, 4.83) 0.84 (0.38, 1.85)	34839 18959 8431 2324 5070	13783 5735 2364 723 1837	54 20 8 6 7	14.3 10.1 9.2 24.8 12.9	hnol	ço N
	ad&Neck cancer Exercise frequency: None (Reference) Secroise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: Altimos/weak Exercise frequency: Altimost everyday	.===	1.00 (1.00, 1) 0.62 (0.39, 0) 0.77 (0.43, 1) 0.49 (0.12, 2) 0.97 (0.48, 1)	96) 51538 38) 19850 03) 4161	18407 13815 5027 1209 2200	59 30 14 2 9	10.8 5.6 6.9 4.6 11.9		÷	1.00 (1.00, 1.00) 0.99 (0.62, 1.58) 0.79 (0.39, 1.60) 1.12 (0.40, 3.07) 1.03 (0.54, 1.95)	34839 18959 8431 2324 5070	13783 5735 2364 723 1837	71 25 9 4 11	18.9 12.6 10.3 16.5 20.5	nologies	025 a
8	iney canoer Exercise frequency: 1-2 timos/week Exercise frequency: 1-2 timos/week Exercise frequency: 3-4 timos/week Exercise frequency: Altimos/week Exercise frequency: Altimost everyday		1.00 (1.00, 1) 1.19 (0.76, 1) 1.41 (0.02, 2) 1.54 (0.61, 3) 0.96 (0.40, 2)	85) 51538 42) 19850 94) 4161	18407 13815 5027 1209 2200	38 44 21 5 6	6.9 8.2 10.3 11.6 7.9	; •		1.00 (1.00, 1.00) 1.73 (0.93, 3.25) 0.66 (0.20, 2.20) 0.00 (0.00, 0.00) 2.37 (1.10, 5.12)	34839 18959 8431 2324 5070	13783 5735 2364 723 1837	25 18 3 9	6.7 9.1 3.4 0 16.7	,	at Ag
	Ibladder cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: Altmost everyday		1.00 (1.00, 1) 0.89 (0.42, 1) 0.88 (0.32, 2) 0.76 (0.10, 5) 1.22 (0.41, 3)	89) 51538 41) 19850 76) 4161	18407 13815 5027 1209 2200	17 12 5 1 4	3.1 2.2 2.4 2.3 5.3			1.00 (1.00, 1.00) 0.48 (0.17, 1.40) 0.72 (0.21, 2.40) 1.49 (0.35, 6.34) 1.37 (0.58, 3.34)	34839 18959 8431 2324 5070	13783 5735 2364 723 1837	27 4 3 2 6	7.2 2 3.4 8.2 11.1		gence
	ophagus cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 timos/week Exercise frequency: 5-8 timos/week Exercise frequency: Almost everyday	;	1.00 (1.00, 1. 0.73 (0.40, 1. 0.57 (0.22, 1. 0.00 (0.00, 0. 0.96 (0.37, 2.	33) 51538 49) 19850 00) 4161	18407 13815 5027 1209 2200	33 17 5 5 5	6 3.2 2.4 0 6.6			1.00 (1.00, 1.00) 1.22 (0.77, 1.94) 0.81 (0.39, 1.71) 0.60 (0.15, 2.44) 1.08 (0.58, 2.00)	34839 18959 8431 2324 5070	13783 5735 2364 723 1837	74 26 8 2 12	19.6 13.1 9.2 8.2 22.2		Bibl
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Crude rate 47,4 48,8 35,8 53,5 54,3 244 68 24 37

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No family history of cancer

Family history of can

	ranny mstor	y or can					i anny mstory		UT I			
Group		HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Crude rate		HR (95% CI)	Gotal Bases(N)	Unique participants(n)	Events(n)	Crud rate
omach cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.89 (0.82, 0.96) 0.84 (0.76, 0.94) 0.92 (0.76, 1.11) 0.89 (0.79, 1.01)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	2325 937 384 111 282	62.4 48.7 49.1 58.8 70.2		1.00 (1.00, 1.00) 1.00 (0.84, 1.15) 1.00 (0.80, 1.24) 0.99 (0.68, 1.46) 0.82 (0.60, 1.15)	0 162185 14350 256872 4093 4093 4093 4093 4093 4093	19431 9600 4261 1105 2191	347 223 105 28 46	63.2 64 65.8 68.2 67.8
olon cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-4 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 1.06 (0.96, 1.17) 1.01 (0.88, 1.16) ◆ 1.14 (0.90, 1.45) 1.01 (0.86, 1.18)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	1247 583 247 74 171	33.3 30.2 31.5 39.1 42.4		1.00 (1.00, 1.00) 0.99 (0.77, 1.26	7	19431 9600 4261 1105 2191	177 109 67 16 20	32.1 31.1 41.9 38.8 29.3
ectum cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-4 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.98 (0.85, 1.12) 0.85 (0.70, 1.03) ◆ 1.02 (0.74, 1.41) 0.99 (0.80, 1.23)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	715 327 124 39 96	19.1 16.9 15.8 20.6 23.7		1.00 (1.00, 1.00) 0.85 (0.60, 1.21) 1.02 (0.67, 1.54) 0.88 (0.41, 1.90) 0.68 (0.36, 1.22)	4350	19431 9600 4261 1105 2191	94 51 30 7 11	17 14.5 18.7 16.9 16.7
ing cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-4 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.92 (0.84, 1.01) 0.81 (0.71, 0.92) 0.80 (0.63, 1.02) 0.94 (0.82, 1.08)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	1908 689 258 70 243	51.1 35.7 32.9 36.9 60.3		1.00 (1.00, 1.00) 0.78 (0.61, 0.98) 0.77 (0.56, 1.09) 0.87 (0.51, 1.42) 0.84 (0.58, 1.23)	02185 04350 05872 1093 1093 10587	19431 9600 4261 1105 2191	230 107 49 15 32	41.7 30.8 30.0 36.2 46.9
ver cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-4 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.96 (0.86, 1.06) 0.88 (0.77, 1.02) 0.91 (0.71, 1.18) 0.94 (0.80, 1.11)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	1271 588 231 62 159	34 30.4 29.4 32.7 39.4		1.00 (1.00, 1.00 0.92 (0.71, 1.20 0.69 (0.47, 1.0 1.06 (0.60, 1.80 0.83 (0.52, 1.3)	4093 6587	19431 9600 4261 1105 2191	152 92 32 13 20	27.5 26.2 19.9 31.4 29.2
Increas cancer Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 1.06 (0.88, 1.28) ↓ 1.12 (0.88, 1.43) ↓ 1.03 (0.66, 1.62) 0.97 (0.73, 1.30)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	415 171 80 20 53	11.1 8.8 10.2 10.5 13.1		A 1.00 (1.00, 1.00) 0.81 (0.53, 1.24 0.58 (0.31, 1.04 0.70 (0.25, 1.94) 0.62 (0.29, 1.34)	2185 4350 5872 093 587	19431 9600 4261 1105 2191	68 34 12 4 7	12.3 9.7 7.5 9.6 10.2
sad&Neck cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.77 (0.62, 0.95) 0.88 (0.66, 1.16) 0.57 (0.31, 1.08) ◆ 0.95 (0.69, 1.31)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	338 125 59 10 43	9 6.5 7.5 5.3 10.6		0.72 (0.41, 1.20) 1.18 (0.64, 2.19) 1.18 (0.63, 4.06) 0.72 (0.26, 2.03)	2185 24350 5872 093 587	19431 9600 4261 1105 2191	39 19 14 5 4	7.1 5.4 8.7 12.7 5.8
dney cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.89 (0.71, 1.11) 1.18 (0.90, 1.55) 1.00 (0.59, 1.72) 1.16 (0.83, 1.63)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	264 120 66 14 39	7.1 6.2 8.4 7.4 9.7		1.00 (1.00, 1.00) 1.27 (0.79, 2.0 a) 0.72 (0.35, 1.5 f) 0.61 (0.15, 2.5 a) 0.82 (0.32, 2.1 c)	02185 34350 15872 1993 587	19431 9600 4261 1105 2191	37 33 9 2 5	6.7 9.4 5.6 4.8 7.3
allbladder cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.91 (0.69, 1.22) 1.11 (0.78, 1.59) 1.63 (0.96, 2.77) 1.25 (0.86, 1.81)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	200 67 37 15 33	5.3 3.5 4.7 7.9 8.1		1.00 (1.00, 1.00) 1.44 (0.73, 2.80) 1.06 (0.42, 2.60) 0.61 (0.08, 4.60) 1.82 (0.72, 4.60)	e 32185 34350 2093 5872 2093 587	19431 9600 4261 1105 2191	19 16 6 1	3.4 4.5 3.7 2.4 8.7
ophagus cancer Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-4 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.86 (0.64, 1.15) 0.82 (0.54, 1.25) ● 0.68 (0.30, 1.53) ● 0.98 (0.65, 1.47)	351171 186251 76877 18364 38451	128853 53323 20575 5571 12944	193 64 26 6 27	5.1 3.3 3.3 3.2 6.7		1.00 (1.00, 1.00) 0.79 (0.38, 1.68)	at 52185 A4350 Agenge 093 587 C	19431 9600 4261 1105 2191	21 11 3 0 1	3.8 3.1 1.9 0 1.5
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Group	Men	HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Crude rate	Women	HR (95% CI)		Unique participants(n)	Events(n)	Cru rate
Stomach cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday	*	1.00 (1.00, 1.00) 0.89 (0.82, 0.97) 0.87 (0.78, 0.98) 0.93 (0.76, 1.14) 0.84 (0.73, 0.97)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	1762 893 363 101 228	87.7 58.6 62.5 77.7 90.9		1.00 (1.00, 1.0 0.95 (0.83, 1.0 0.87 (0.72, 1.0 0.92 (0.67, 1.9 0.96 (0.78, 1.1 0.96	590 ²¹³¹⁶⁸ 73310 0 35787 0 9823 1 20954 3	83300 23072 10563 3144 7626	910 267 126 38 100	40. 35. 35 38 45.
Zolon cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 5-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 1.10 (0.98, 1.24) 1.01 (0.86, 1.18) 1.12 (0.85, 1.47) 0.97 (0.80, 1.18)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	779 500 194 56 122	38.5 32.7 33.2 42.9 48.3		1.00 (1.00, 1.00 0.94 (0.80, 1.10) 1.14 (0.93, 1.30) 1.14 (0.81, 1.60) 0.94 (0.73, 1.24)	0 0 9823 → 20954	83300 23072 10563 3144 7626	645 192 120 34 69	28. 25. 33. 34 31.
Rectum cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 6-8 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 1.04 (0.89, 1.21) 0.91 (0.74, 1.13) 0.92 (0.62, 1.36) 1.11 (0.87, 1.41)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	455 285 105 27 79	22.4 18.6 17.9 20.6 31.2		1.00 (1.00, 1.0) 0.83 (0.65, 1.0) 0.84 (0.63, 1.1) 1.16 (0.73, 1.84) 0.69 (0.47, 1.0)	2019 35787 02019 2019	83300 23072 10563 3144 7626	354 93 49 19 28	15. 12. 13. 19 12.
Lung cancer Exarcise frequency: None (Reference) Exarcise frequency: 1-2 times/week Exarcise frequency: 5-4 times/week Exarcise frequency: 5-6 times/week Exarcise frequency: Almost everyday		1.00 (1.00, 1.00) 0.86 (0.78, 0.95) 0.76 (0.66, 0.87) 0.72 (0.55, 0.94) 0.90 (0.78, 1.04)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	1500 602 219 57 207	74.4 39.4 37.5 43.6 82.2		1.00 (1.00, 1.0 1.04 (0.89, 1.2 0.93 (0.74, 1.1 1.04 (0.71, 1.5 0.96 (0.75, 1.2 0.96 (0.75, 1.2 0.97 (0.75, 1.2) 0.97 (0.75, 1	035787 0309823 20954	83300 23072 10563 3144 7626	638 194 88 28 68	28. 25. 24. 28 31
Liver cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: S-6 times/week Exercise frequency: Atimost everyday		1.00 (1.00, 1.00) 0.96 (0.86, 1.06) 0.88 (0.75, 1.02) 0.83 (0.62, 1.10) 0.89 (0.74, 1.08)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	987 559 210 50 127	48.8 36.6 36 38.2 50.3		1.00 (1.00, 1.00) 0.93 (0.76, 1.13) 0.79 (0.59, 1.05) 1.32 (0.88, 1.93) 1.05 (0.78, 1.44)	C 1213168 73310 9823 20954	83300 23072 10563 3144 7626	436 121 53 25 52	19. 16. 14. 25 23.
Pancreas cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-4 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 1.09 (0.88, 1.35) 1.21 (0.91, 1.59) 0.90 (0.52, 1.58) 0.69 (0.46, 1.03)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	249 140 65 13 27	12.2 9.1 11.1 9.9 10.6		1.00 (1.00, 1.00) 0.93 (0.70, 1.20) 0.75 (0.50, 1.19) 1.07 (0.59, 1.94) 1.26 (0.87, 1.84)	213168 73310 35787 9823 20954	83300 23072 10563 3144 7626	234 65 27 11 33	10. 8.6 7.5 11 15
Head&Neck cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Atmost everyday		1.00 (1.00, 1.00) 0.74 (0.59, 0.92) 0.87 (0.65, 1.16) 0.68 (0.37, 1.25) 0.94 (0.67, 1.33)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	276 116 55 11 38	13.6 7.6 9.4 8.4 15		a 1.00 (1.00, 1.0 0.87 (0.57, 1.3 1.11 (0.67, 1.8 0.88 (0.32, 2.6 0.82 (0.41, 1.6 a	213168 73310 35787 9823 20954	83300 23072 10563 3144 7626	101 28 18 4 9	4.4 3.7 5 4 4.1
Kidney cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Almost everyday		1.00 (1.00, 1.00) 0.88 (0.70, 1.12) 0.96 (0.70, 1.31) 0.89 (0.49, 1.64) 1.22 (0.84, 1.75)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	194 113 49 11 34	9.6 7.4 8.4 8.4 13.4		1.00 (1.00, 1.0 1.14 (0.79, 1.6 1.45 (0.94, 2.2 0.99 (0.40, 2.4 0.83 (0.43, 1.5	0213168 73310 35787 9823 020954	83300 23072 10563 3144 7626	107 40 26 5 10	4.7 5.3 7.2 5 4.6
Galibladder cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-6 times/week Exercise frequency: Atimost everyday		1.00 (1.00, 1.00) 0.81 (0.56, 1.16) 0.89 (0.55, 1.44) 1.43 (0.72, 2.85) 1.48 (0.95, 2.31)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	101 44 21 9 25	5 2.9 3.6 6.9 9.8		1.00 (1.00, 1.0) 1.20 (0.83, 1.7 1.33 (0.84, 2.1 1.48 (0.69, 3.1 1.06 (0.61, 1.8 0	213168 73310 9823 9823 20954	83300 23072 10563 3144 7626	118 39 22 7 14	5.2 5.2 6.1 7 6.4
Esophagus cancer Exercise frequency: None (Reference) Exercise frequency: 1-2 times/week Exercise frequency: 3-4 times/week Exercise frequency: 5-4 times/week Exercise frequency: Atmost everyday		1.00 (1.00, 1.00) 0.86 (0.65, 1.15) 0.76 (0.50, 1.16) 0.64 (0.28, 1.45) 0.97 (0.64, 1.45)	190188 147291 56962 12634 24084	64984 39851 14273 3532 7509	184 68 25 6 27	9 4.4 4.3 4.6 10.6		1.00 (1.00, 1.00 0.83 (0.36, 1.94 0.93 (0.32, 2.6 0 0.00 (0.00, 0.0 9 0.31 (0.04, 2.27)	20213168 773310 35787 at 20954	83300 23072 10563 3144 7626	30 7 4 0 1	1.3 .9 1.1 0 .5

Supplementary Figure 5. Results from running Cox regression models examining effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequenc gand various incident cancer outcomes. Note: Cox regression models using age as the underlying timescale were adjusted for sex [not in models for effect]

 BMJ Open modification by sex], body mass index [not in models for effect modification by body mass index], systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of cancer [not in models for effect modification by family history of cancer]. smoking status [not in models for effect modification by smoking status] and alcohol consumption [not in Eno modification by alcohol consumption]. Crude rates are per 100,000 person-years. "N" indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and "n" indicates numbers of unique participants at baseline. P-values for multiplicative terms – stomach cancer (p-value = 0.274), colon cancer (p-value $\frac{1}{2}$ $p = \frac{1}{2}$ value = 0.107), lung cancer (p-value = 0.016), liver cancer (p-value = 0.129), pancreas cancer (p-value = 0.016), head & neck cancer (p-value = 0.488), kidney cancer (p-value = 0.285), gallbladder cancer (p-value = 0.970), and es a la cancer (p-value = 0.263) by body mass index; stomach cancer (p-value = 0.699), colon cancer (p-value = 0.932), rectum caite (p-value = 0.610), lung cancer (p-value = 0.492), liver cancer (p-value = 0.405), pancreas cancer (p-value = 0.338), head & nec **£** definer (p-value = 0.562), kidney cancer (p-value = 0.280), gallbladder cancer (p-value = 0.295), and esophagus cancer (p-value = (p-value) by smoking; stomach cancer (p-value = 0.655), colon cancer (p-value = 0.977), rectum cancer (p-value = 0.433), lun liver cancer (p-value = 0.704), pancreas cancer (p-value = 0.711), head & neck cancer (p-value = 1.000) 0.336), gallbladder cancer (p-value = 0.350), and esophagus cancer (p-value = 0.550) by alcohol consuming is stomach cancer (pvalue = 0.996), colon cancer (p-value = 0.399), rectum cancer (p-value = 0.478), lung cancer (p-value = $\frac{3}{2}$, liver cancer (p-value = 0.337), pancreas cancer (p-value = 0.086), head & neck cancer (p-value = 0.712), kidney cancer (p-vate = 0.319), gallbladder cancer (p-value = 0.766), and esophagus cancer (p-value = 0.098) by family history of cancer; and stomachecancer (p-value = 0.405), colon cancer (p-value = 0.957), rectum cancer (p-value = 0.106), lung cancer (p-value = 0.063), liver cancer $\frac{1}{2}$ p-value = 0.278), pancreas cancer (p-value = 0.265), head & neck cancer (p-value = 0.907), kidney cancer (p-value = 0.967), allbladder cancer (pvalue = 0.548), and esophagus cancer (p-value = 0.256) by sex. Abbreviations: HR – Hazard Ratio; CI - Confidence Intervals

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