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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 non-communicable 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 non-fatal 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.

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 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] diabetes[5] and cancer,[6] has increased dramatically over the past few decades, although age-standardized cardiovascular disease and cancer rates as well as systolic blood pressure levels[7] 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 rates[10] have increased more rapidly, while age-standardized cardiovascular disease rates[3] and systolic blood pressure levels[7] 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-

communicable diseases, such as adiposity levels,[15,16] smoking,[17] glucose levels[18] 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.

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 out-patient 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 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 mmHg, diastolic ≥90 mmHg) and fasting glucose levels (e.g., ≥126 mg/dL), both of which were measured during physical examinations, were used in conjunction with physician 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. 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 above-mentioned 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, ≥25kg^2/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

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 ≥140 mmHg or diastolic ≥90 mmHg), diabetes (additionally, fasting glucose levels ≥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 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 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

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.

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 research[24-26] 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] diabetes[32-39] 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 hypertension[48] 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 hypertension[50-52] 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 ≥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.

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 in-patient 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 diseases[12] 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 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 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

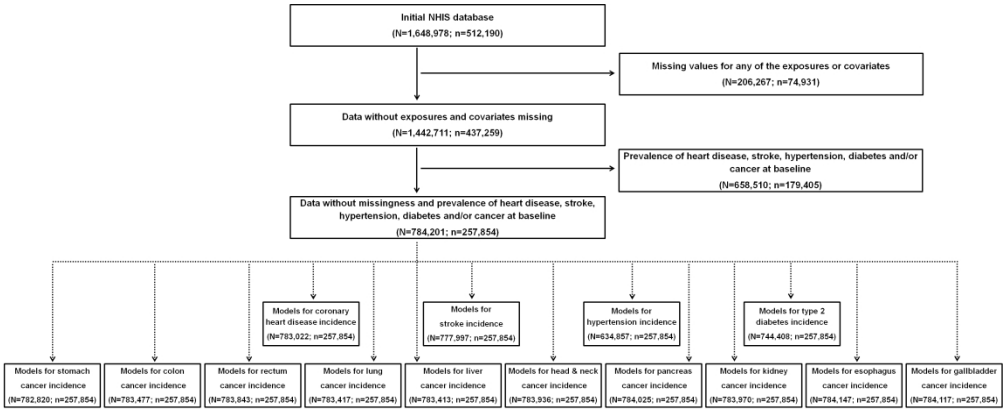
Figure 3. Associations of exercise frequency with various incident cancer outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of cancer, smoking status and 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 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

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 everyday (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 (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)

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 Korean adults (2002-2015) with the entire Korean population’s health insurance system.



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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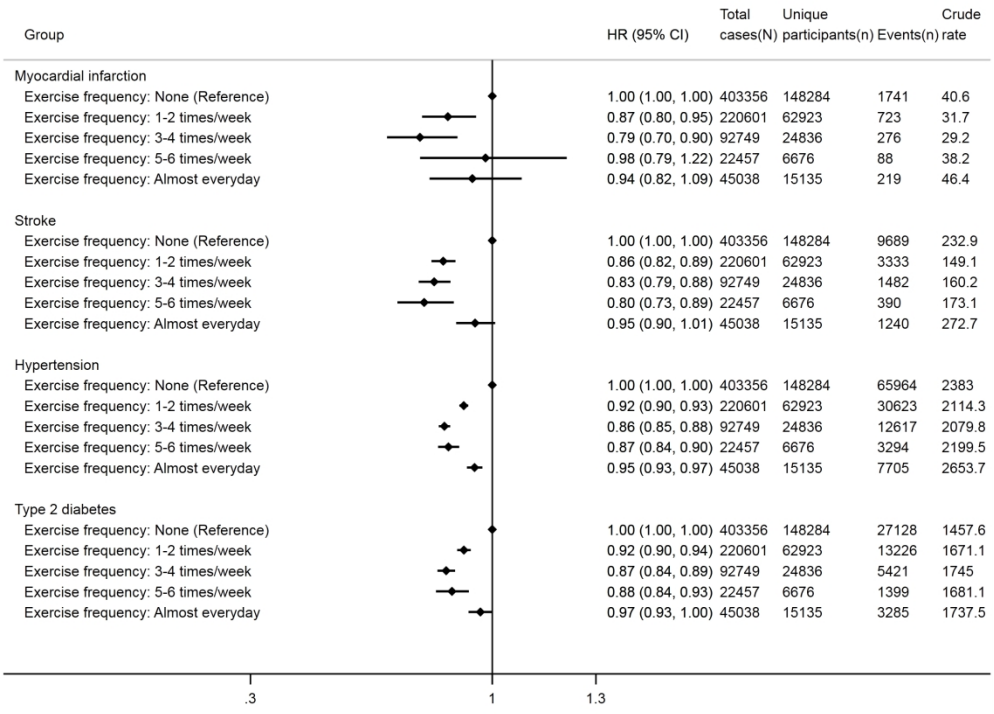

Associations of exercise frequency with various incident cardiovascular disease outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of heart disease, stroke 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

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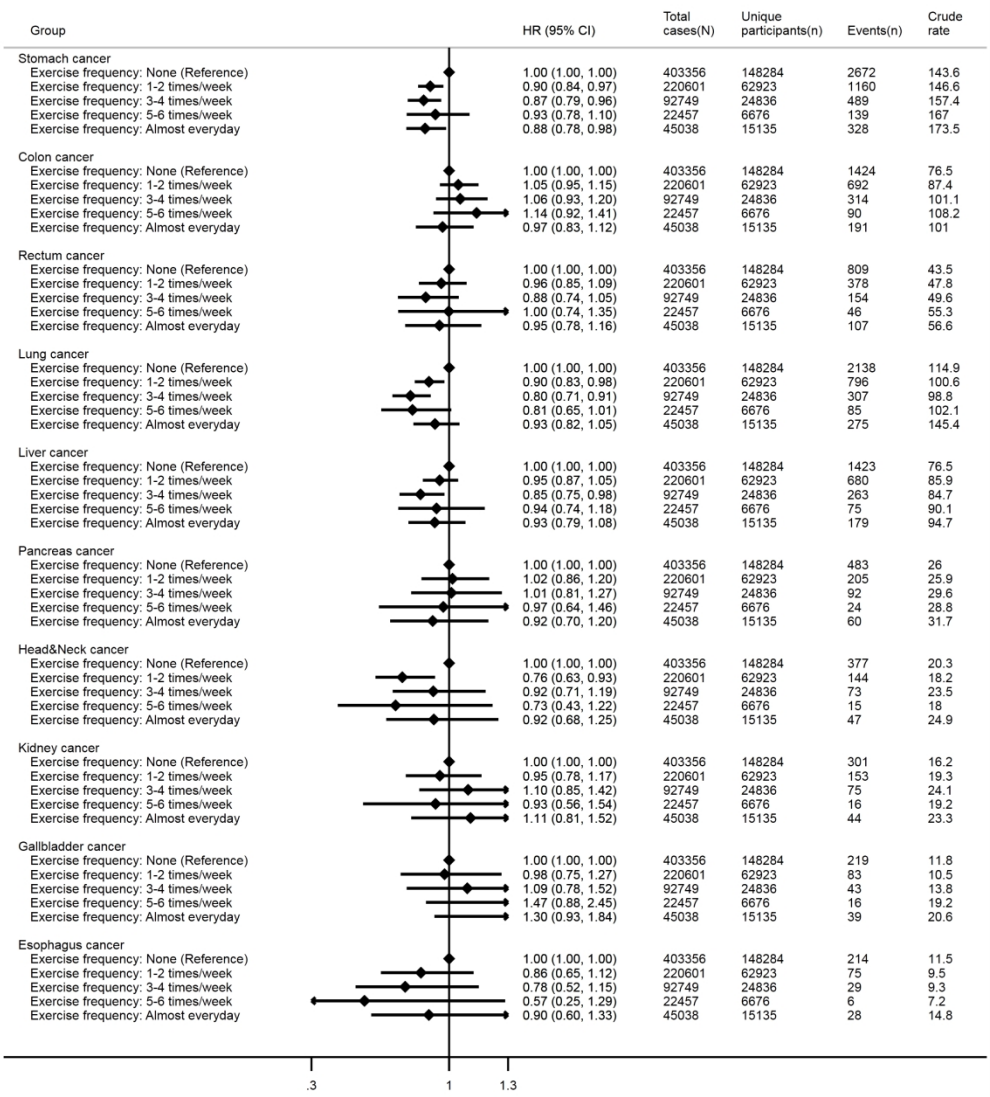

Associations of exercise frequency with various incident cancer outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of cancer, smoking status and alcohol 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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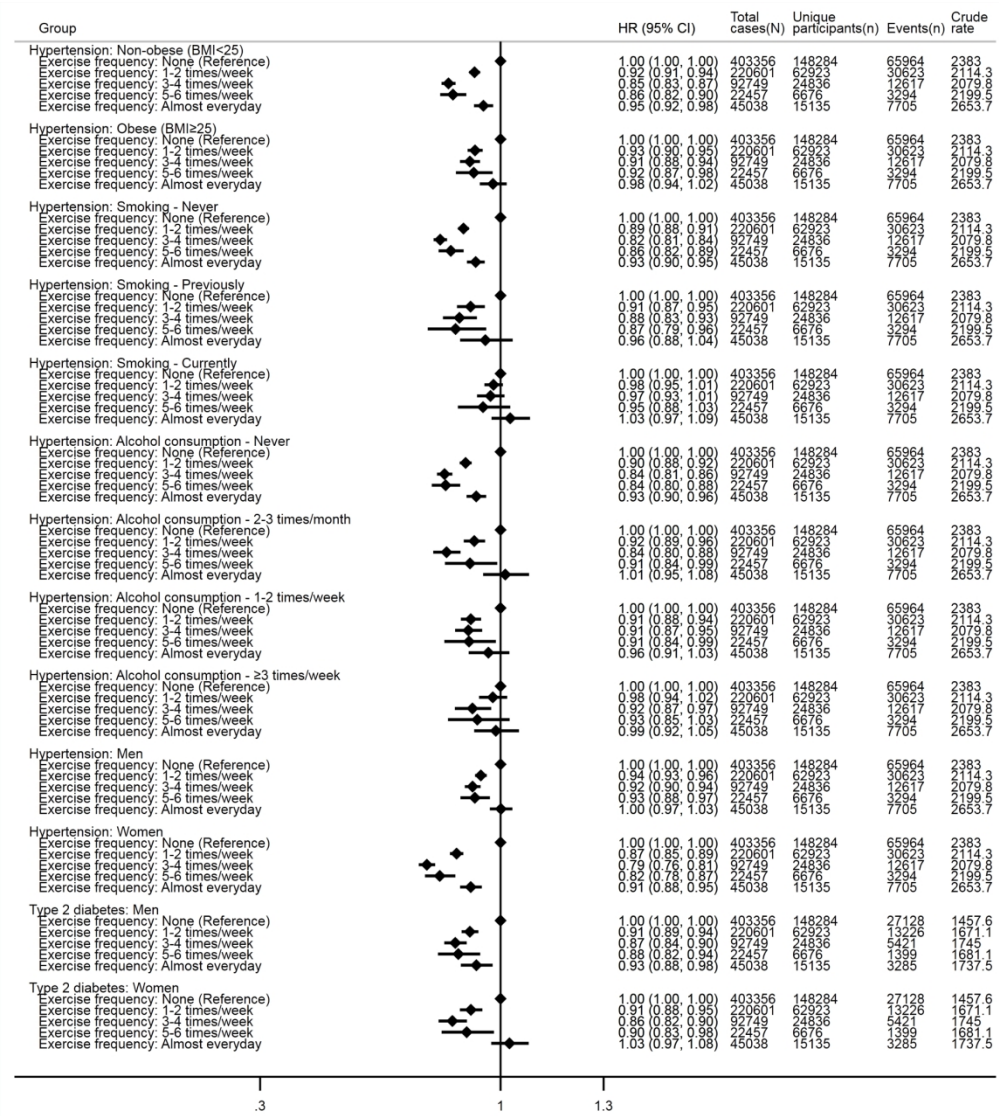


Results from assessment of effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequency and each incident disease outcome. Only associations for which the multiplicative interaction terms were statistically significant 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

Supplementary Table 1. Definitions for classification of incident disease outcomes

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 mmHg, diastolic blood pressure ≥90 mmHg, 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

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

Repeat visit 1st	Variables	All (n=215,295)	Exercise frequency				
			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, 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, mmHg	120.5 (14.4)	120.6 (14.7)	120.4 (13.9)	120.0 (13.9)	119.6 (13.9)	121.4 (14.6)
	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 (36.7)
	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%

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

Repeat visit 2nd	Variables	All (n=150,845)	Exercise frequency				
			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, kg^2/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 (14.5)
	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 (36.5)
	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 3rd	Variables	All (n=80,639)	Exercise frequency				
			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, kg^2/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%

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

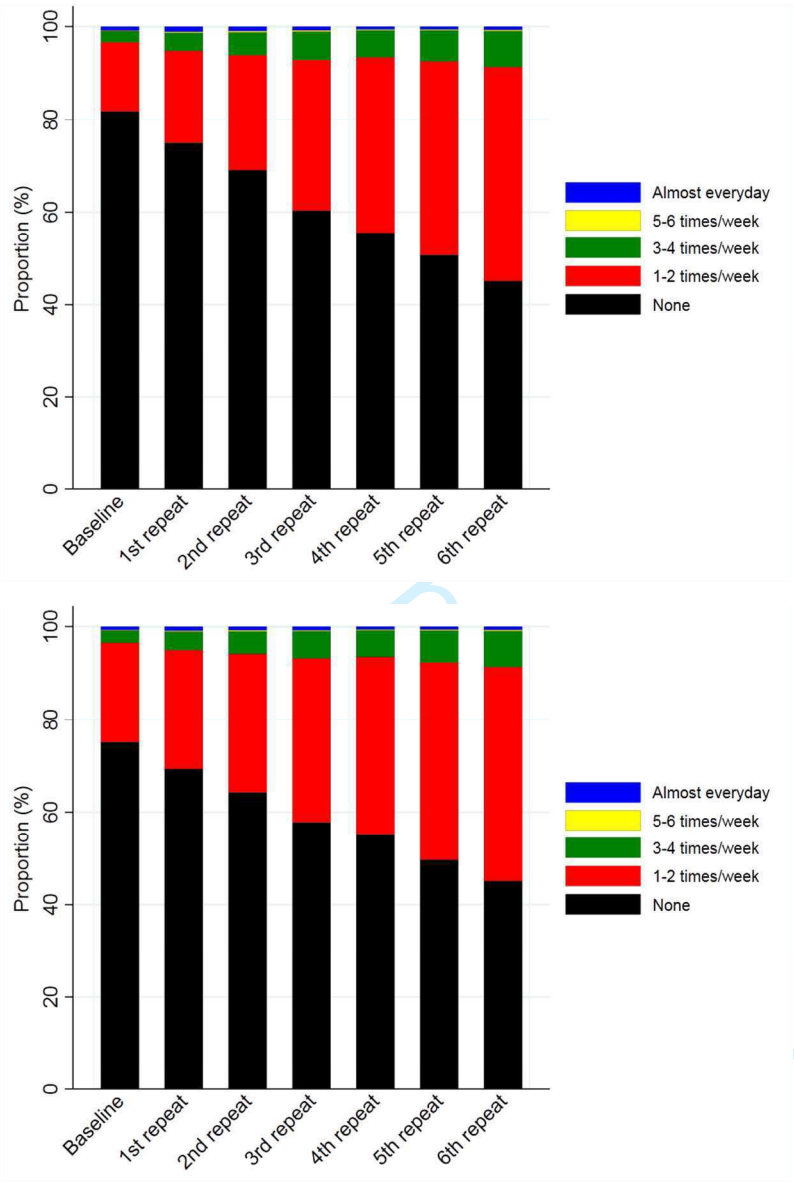
Repeat visit 4th	Variables	All (n=40,910)	Exercise frequency				
			None (n=17,678)	1-2 times/week (n=14,624)	3-4 times/week (n= 5,685)	5-6 times/week (n=1,094)	Almost everyday (n=1,829)
	Sex, %						
	Men	72.3%	61.6%	81.1%	81.5%	78.2%	73.9%
	Women	27.7%	38.4%	18.9%	18.5%	21.9%	26.1%
	Age, years	50.9 (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, kg^2/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%

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

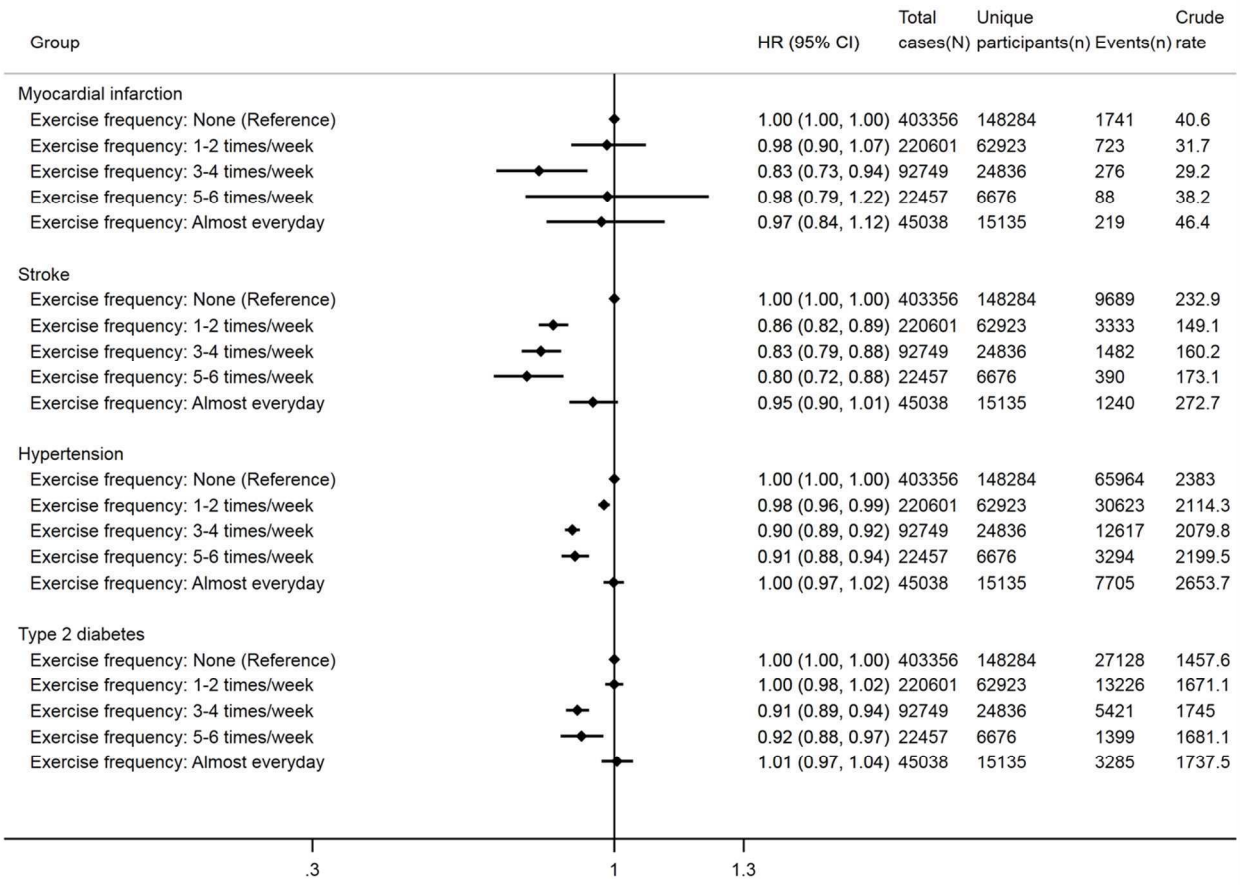
Repeat visit 5th	Variables	All (n= 26,356)	Exercise frequency				
			None (n=10,771)	1-2 times/week (n=9,807)	3-4 times/week (n=3,884)	5-6 times/week (n=724)	Almost everyday (n=1,170)
	Sex, %						
	Men	73.7%	62.6%	81.6%	82.4%	81.2%	76.9%
	Women	26.3%	37.4%	18.4%	17.6%	18.8%	23.0%
	Age, years	51.1 (4.9)	51.4 (5.1)	50.8 (4.7)	51.0 (4.7)	51.4 (5.0)	52.1 (5.6)
	Body Mass Index, kg^2/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 (12.7)
	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 (37.0)
	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%

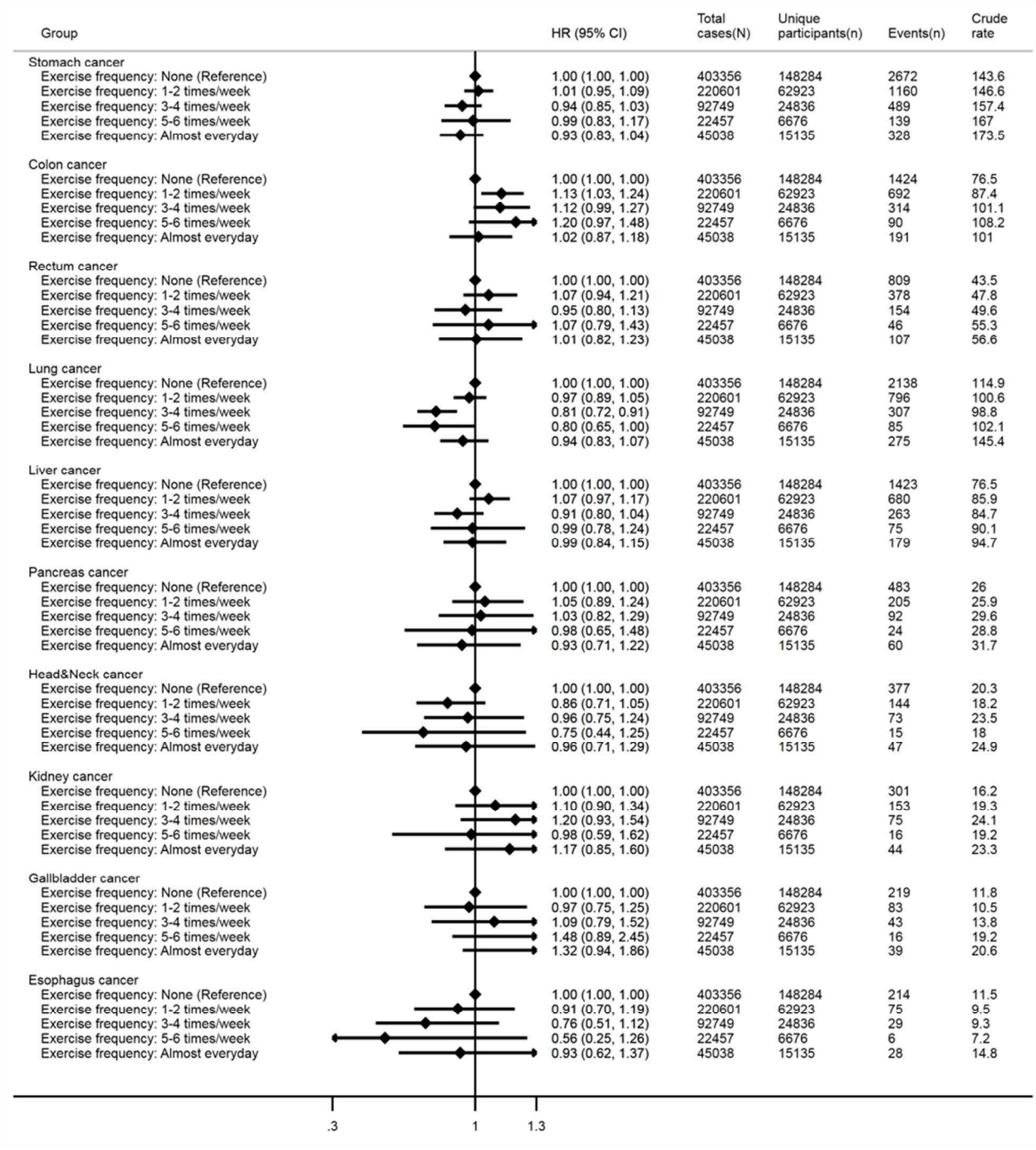
Supplementary Table 2. Participants' characteristics at 1st, 2nd, 3rd, 4th, 5th and 6th repeat-visit (cont.)

Repeat visit 6th	Variables	All (n= 12,302)	Exercise frequency				
			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, 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 (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 (12.3)
	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 (34.3)
	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).





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 non-fatal 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.

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] diabetes[5] and cancer,[6] has increased dramatically over the past few decades, although age-standardised cardiovascular disease and cancer rates as well as systolic blood pressure levels[7] 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 diabetes[10] has increased more rapidly, while the age-standardised prevalence of cardiovascular disease[3]

and systolic blood pressure levels[7] 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 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, 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 levels[18] 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 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 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 out-patient 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' in-patient 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 ≥90 mm Hg) and fasting glucose levels (e.g., ≥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 (interquartile range: 10.2-11.3 years)

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, ≥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, ≥25kg^2/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 ≥140 mm Hg or diastolic ≥90 mm Hg), diabetes (additionally, fasting glucose levels ≥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

(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., ≥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

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 research[25-27] 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] diabetes[33-40] and different type of cancers.[41-47] 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,[48] and linear associations with the incidence of hypertension[49] 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 ≥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 hypertension[51-53] 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 ≥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.

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 in-patient 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 non-communicable diseases[12] 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

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 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 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

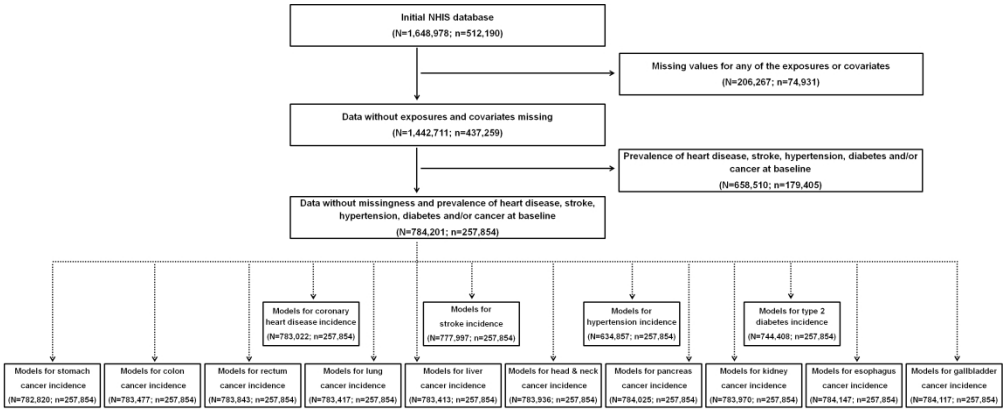
Figure 4. Results from assessment of effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequency and each incident disease outcome. Only associations for which the multiplicative interaction terms were statistically 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) with the entire South 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 everyday (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)

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 adults (2002-2015) with the entire South Korean population’s health insurance system.



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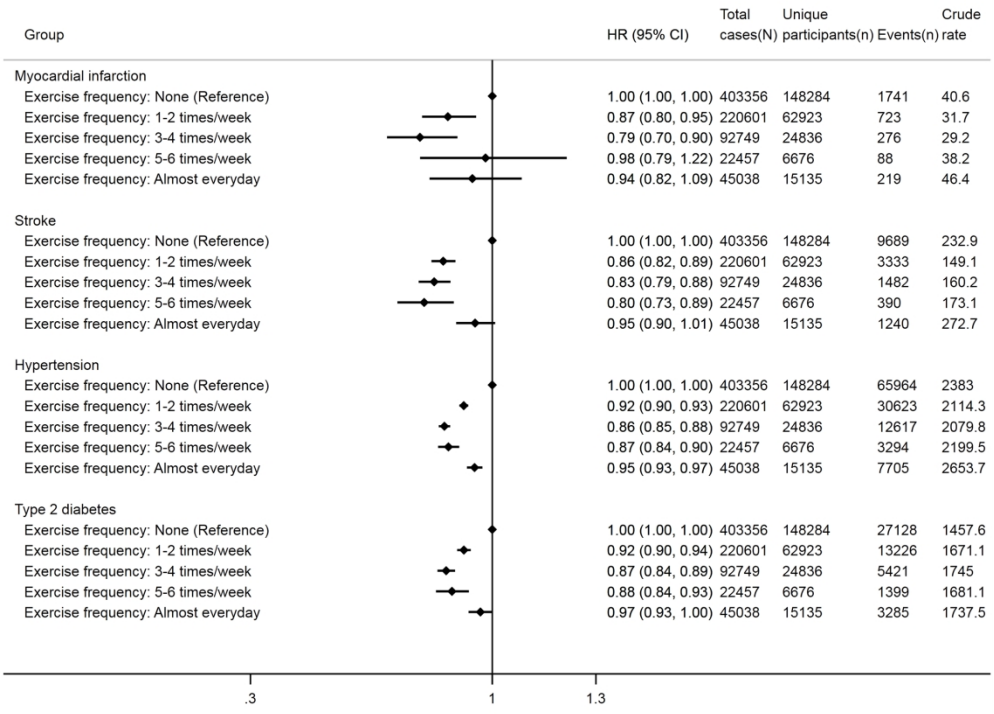

Figure 2. Associations of exercise frequency with various incident cardiovascular disease outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of heart disease, 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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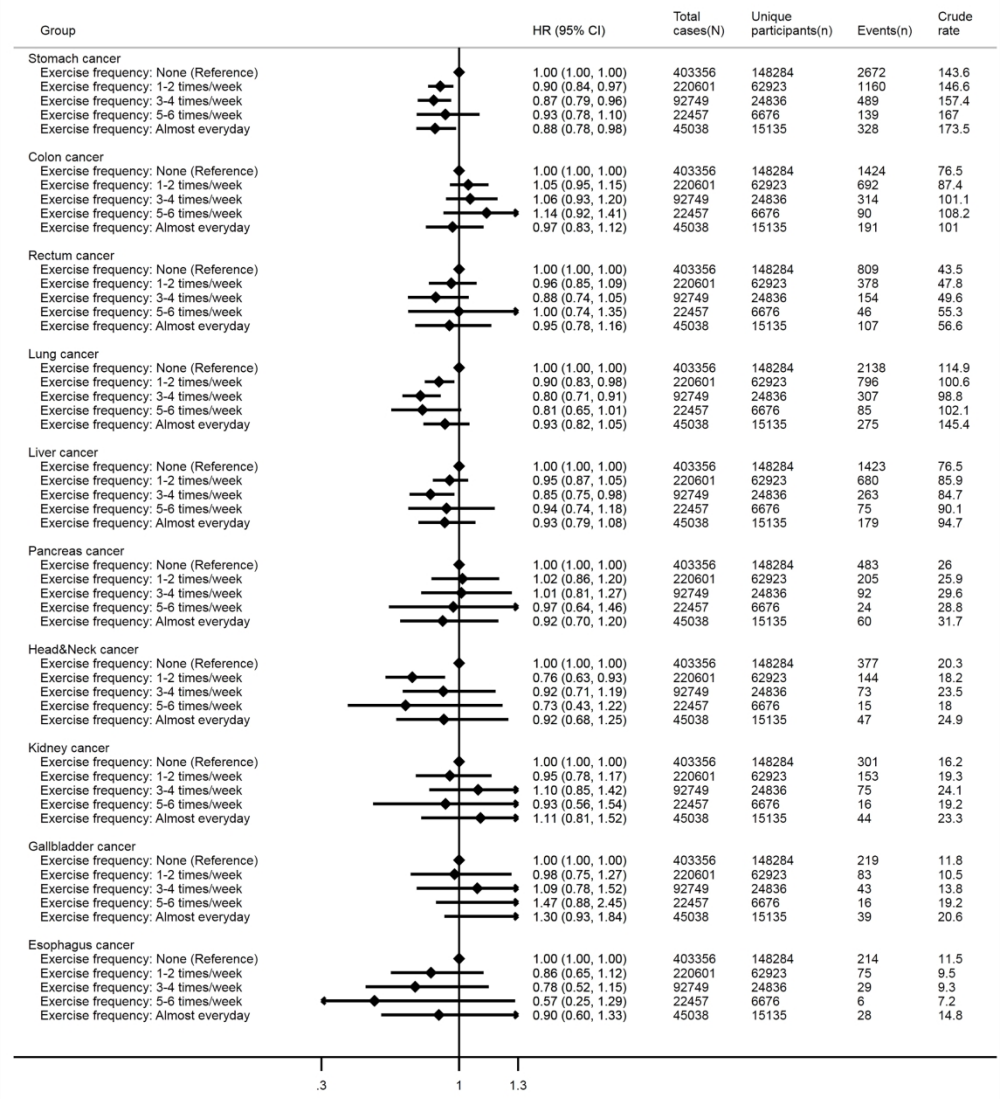

Figure 3. Associations of exercise frequency with various incident cancer outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of cancer, smoking status and 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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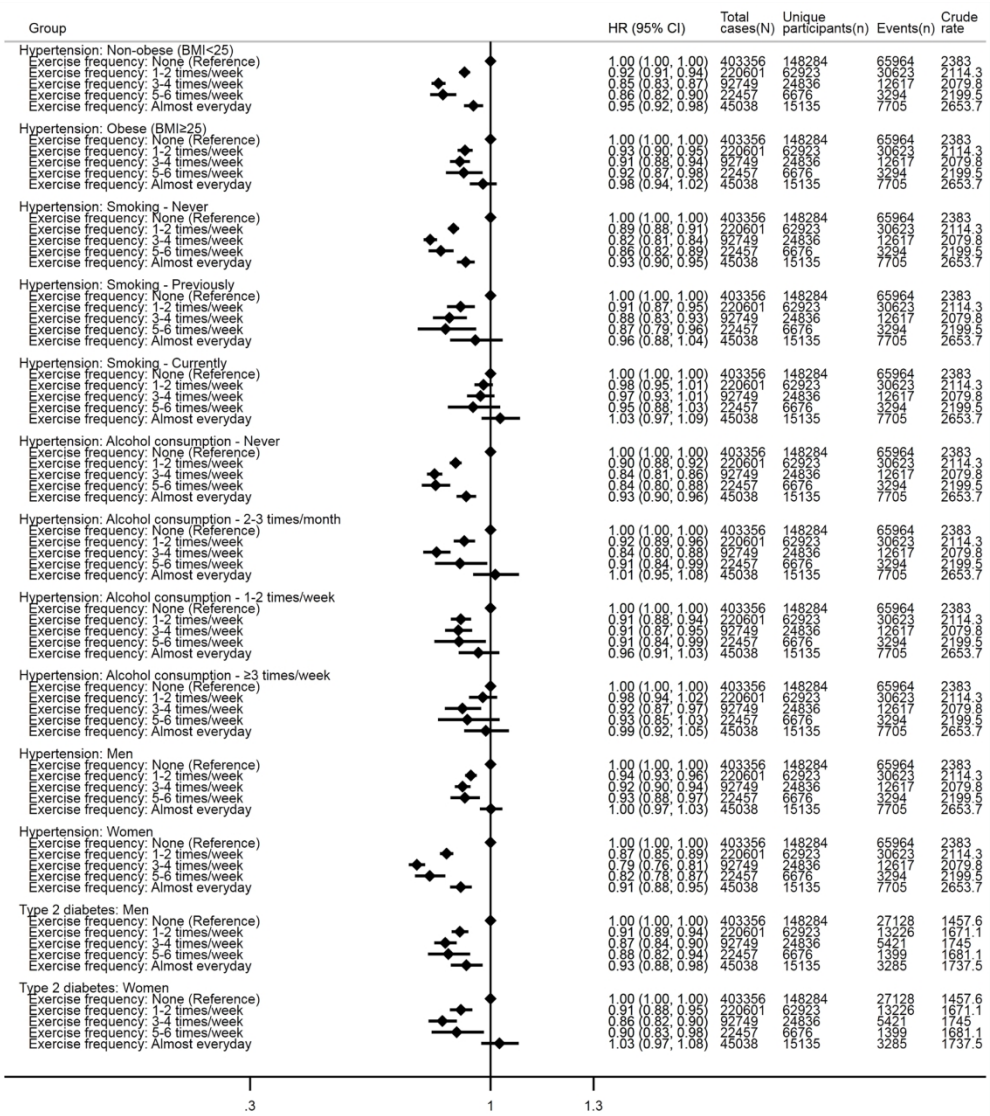


Figure 4. Results from assessment of effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequency and each incident disease outcome. Only associations for which the multiplicative interaction terms were statistically 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

Supplementary Table 1. Definitions for classification of incident disease outcomes

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

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

Repeat visit 1st	Variables	All (n=215,295)	Exercise frequency				
			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, 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	120.5 (14.4)	120.6 (14.7)	120.4 (13.9)	120.0 (13.6)	119.6 (13.9)	121.4 (14.6)
	Diastolic blood pressure, mm Hg	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 (35.8)	197.4 (35.9)	197.8 (36.7)
	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%

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

Repeat visit 2nd	Variables	All (n=150,845)	Exercise frequency				
			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, kg^2/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, mm Hg	120.9 (14.1)	121.0 (14.5)	120.7 (13.7)	120.4 (13.6)	120.3 (13.7)	122.0 (14.5)
	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)	76.0 (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 (36.5)
	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 3rd	Variables	All (n=80,639)	Exercise frequency				
			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, kg^2/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, mm Hg	121.1 (13.6)	120.9 (13.9)	120.9 (13.4)	121.0 (13.6)	120.6 (13.3)	122.0 (14.0)
	Diastolic blood pressure, mm Hg	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 (34.8)	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%

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

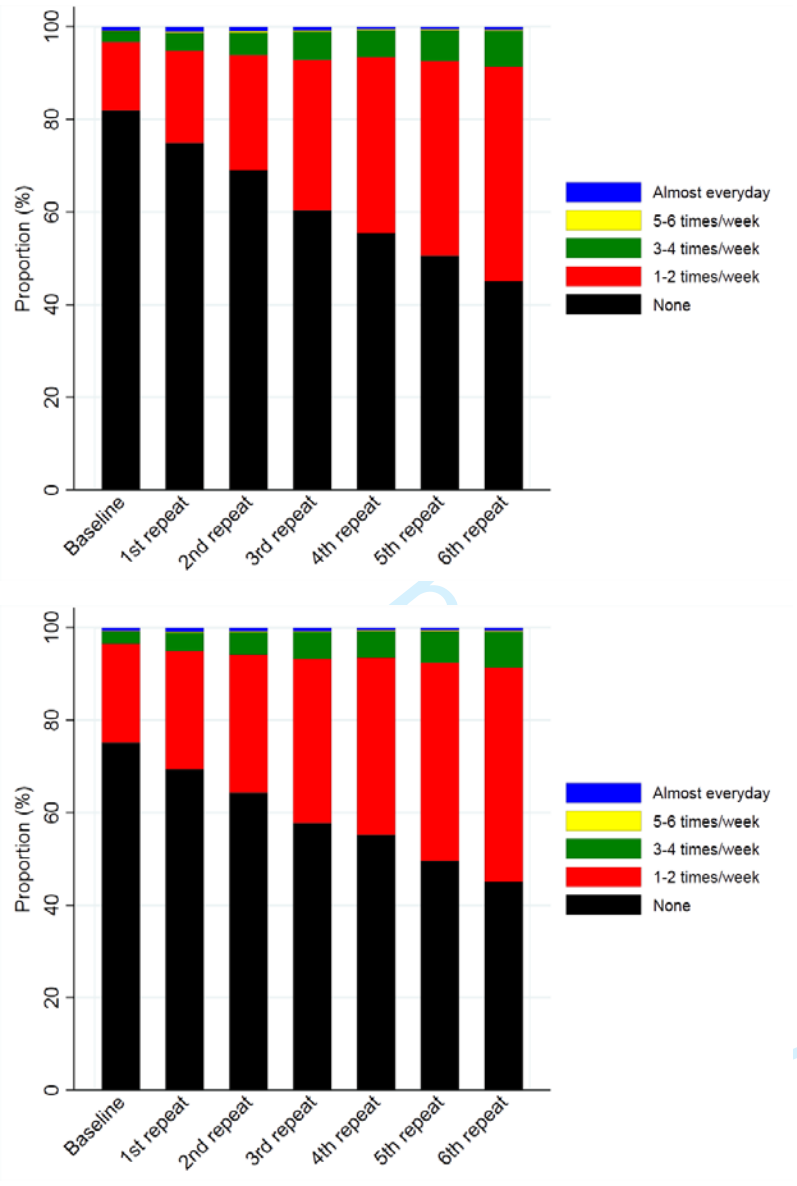
Repeat visit 4th	Variables	All (n=40,910)	Exercise frequency				
			None (n=17,678)	1-2 times/week (n=14,624)	3-4 times/week (n= 5,685)	5-6 times/week (n=1,094)	Almost everyday (n=1,829)
	Sex, %						
	Men	72.3%	61.6%	81.1%	81.5%	78.2%	73.9%
	Women	27.7%	38.4%	18.9%	18.5%	21.9%	26.1%
	Age, years	50.9 (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, kg^2/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, mm Hg	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, mm Hg	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 (34.8)	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%

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

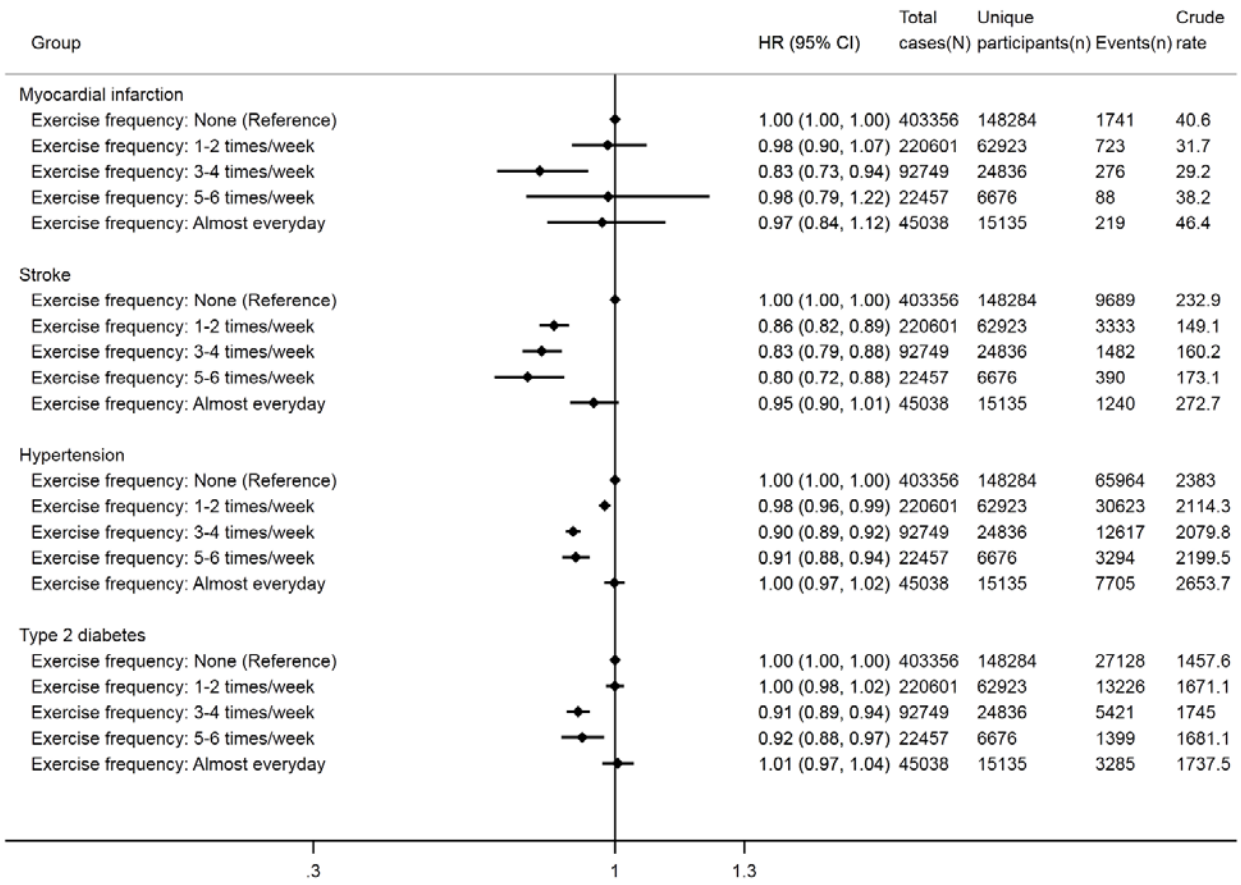
Repeat visit 5th	Variables	All (n= 26,356)	Exercise frequency				
			None (n=10,771)	1-2 times/week (n=9,807)	3-4 times/week (n=3,884)	5-6 times/week (n=724)	Almost everyday (n=1,170)
	Sex, %						
	Men	73.7%	62.6%	81.6%	82.4%	81.2%	76.9%
	Women	26.3%	37.4%	18.4%	17.6%	18.8%	23.0%
	Age, years	51.1 (4.9)	51.4 (5.1)	50.8 (4.7)	51.0 (4.7)	51.4 (5.0)	52.1 (5.6)
	Body Mass Index, kg^2/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, mm Hg	121.4 (13.0)	121.0 (13.4)	121.8 (12.9)	121.6 (12.8)	120.8 (12.9)	121.5 (12.7)
	Diastolic blood pressure, mm Hg	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 (37.0)
	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%

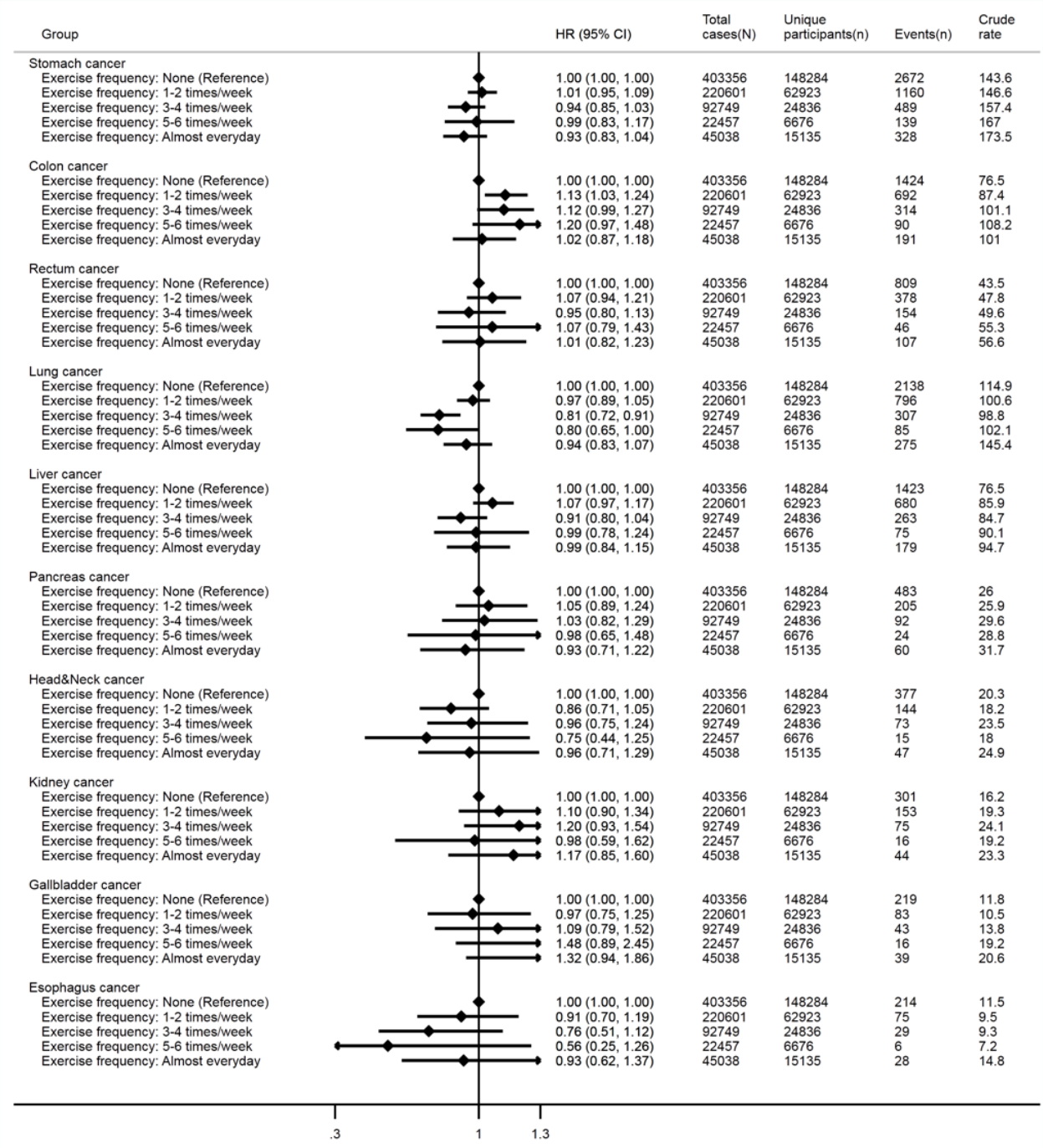
Supplementary Table 2. Participants' characteristics at 1st, 2nd, 3rd, 4th, 5th and 6th repeat-visit (cont.)

Repeat visit 6th	Variables	All (n= 12,302)	Exercise frequency				
			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, 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 (2.5)
	Systolic blood pressure, mm Hg	121.5 (12.8)	121.2 (13.0)	121.6 (12.6)	121.7 (12.8)	121.0 (12.5)	122.1 (12.3)
	Diastolic blood pressure, mm Hg	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 (34.3)
	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%

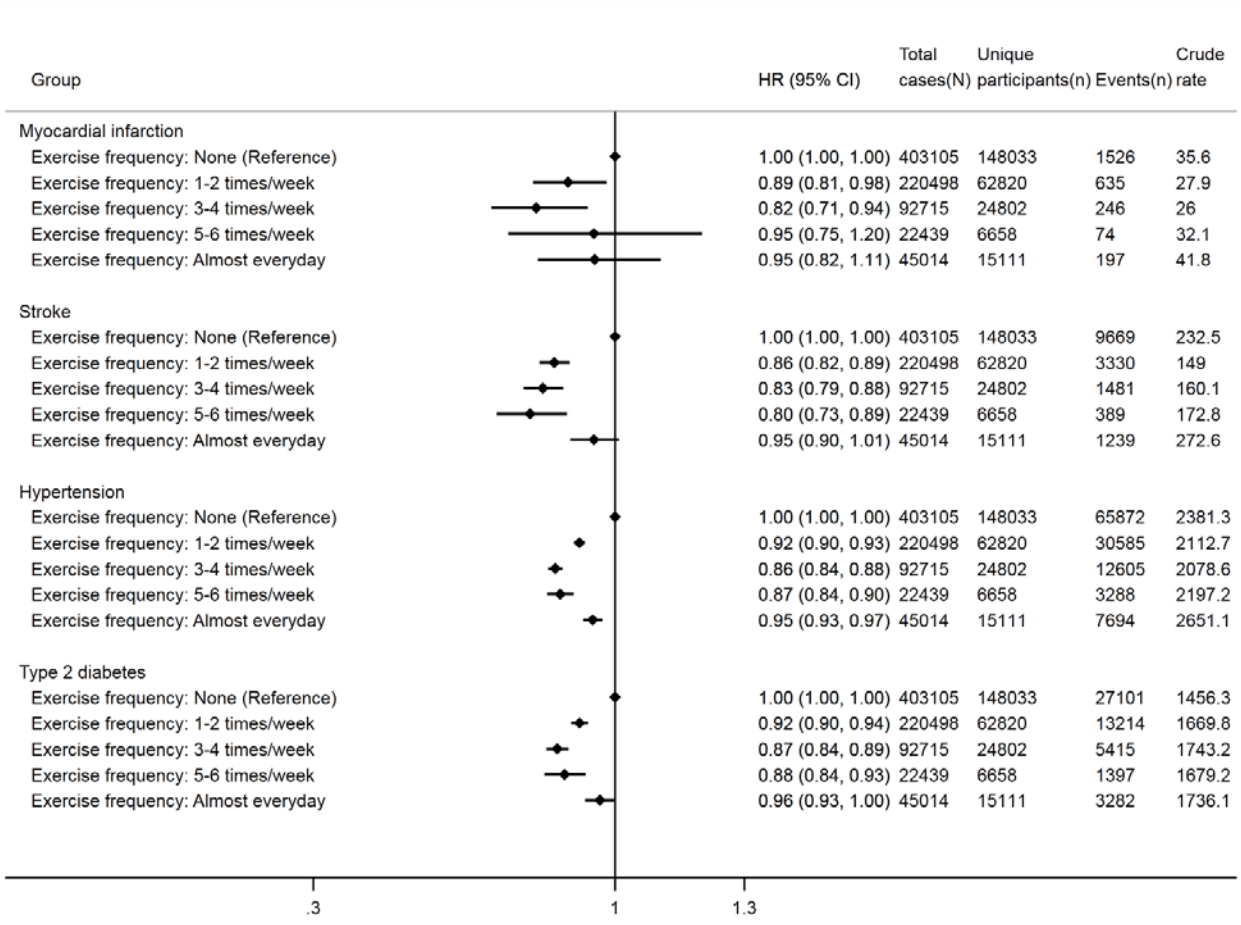


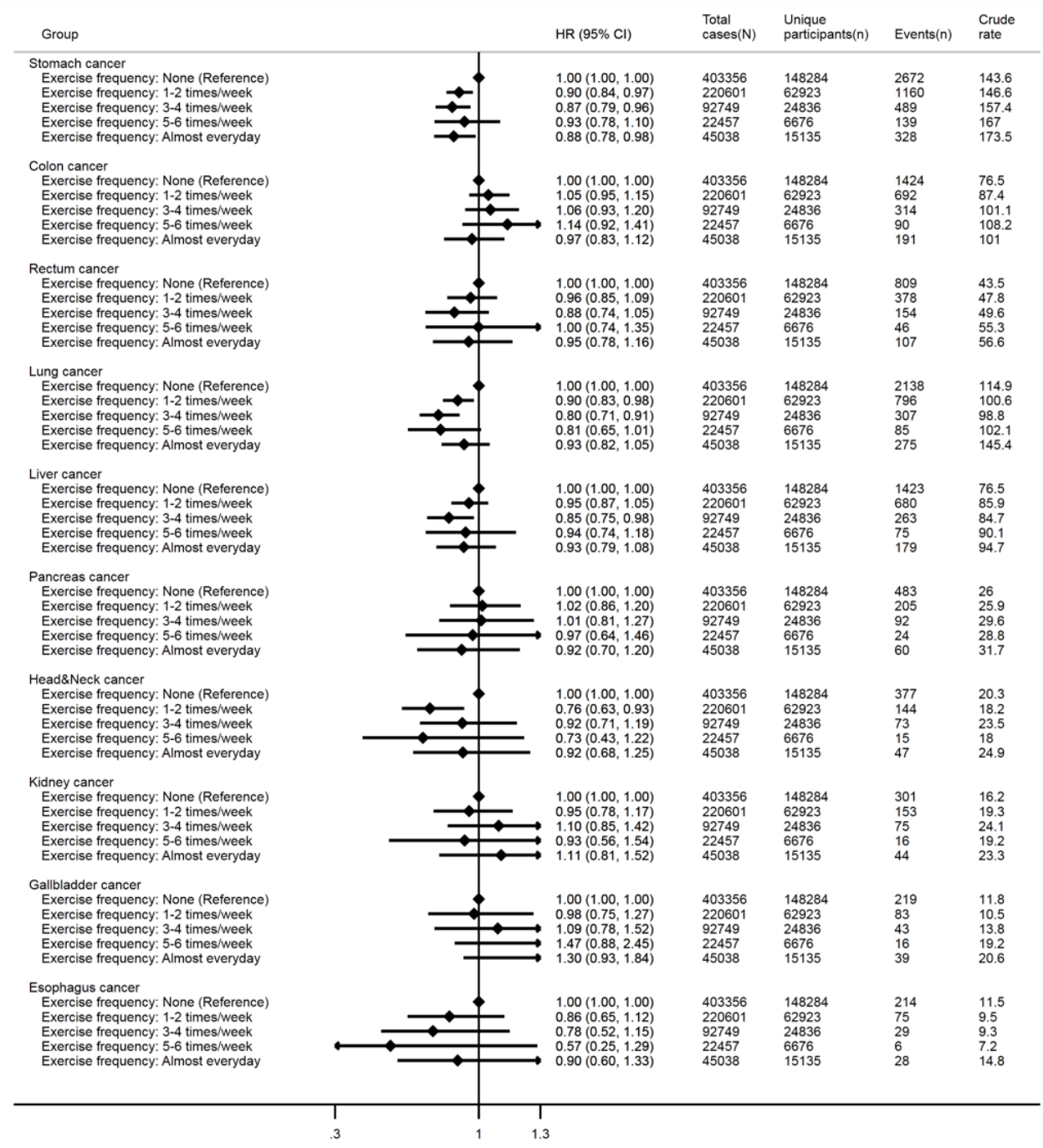
Supplementary Figure 1. Changes in proportions of exercise frequency categories across 7 time points in all 257,854 individuals who provided data at each respective assessment visit (top panel), and 12,302 individuals who provided data from all 7 assessment visits (bottom panel).





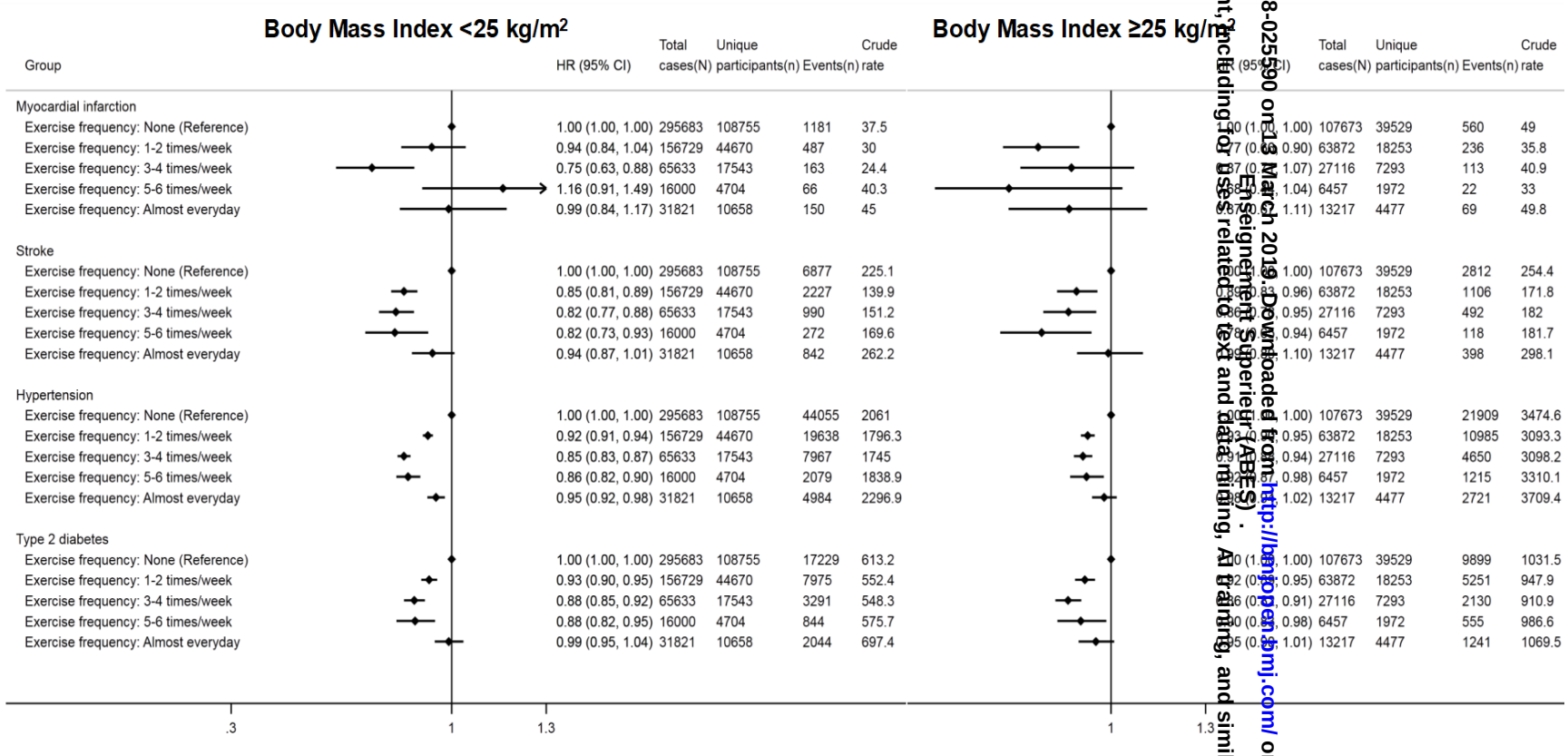
Supplementary Figure 2. Associations of exercise with incident myocardial infarction, stroke, hypertension and Type 2 diabetes (top panel) and various incident cancer outcomes (bottom panel). Note: Cox regression models using age as the underlying timescale were not adjusted for any confounders. Crude 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

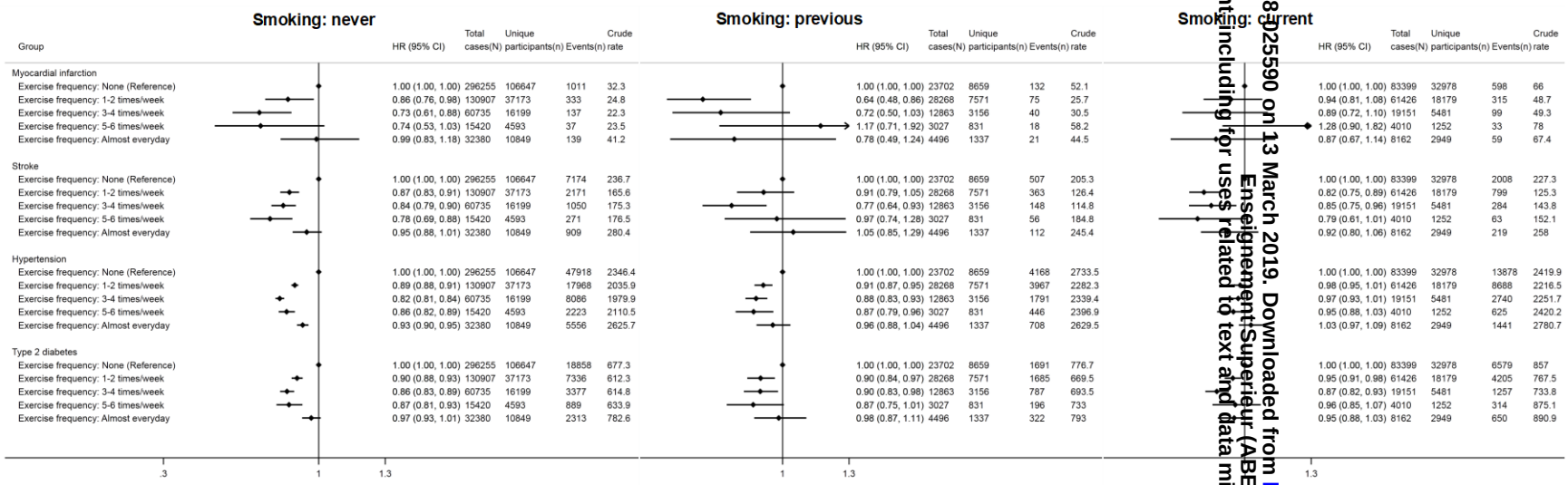


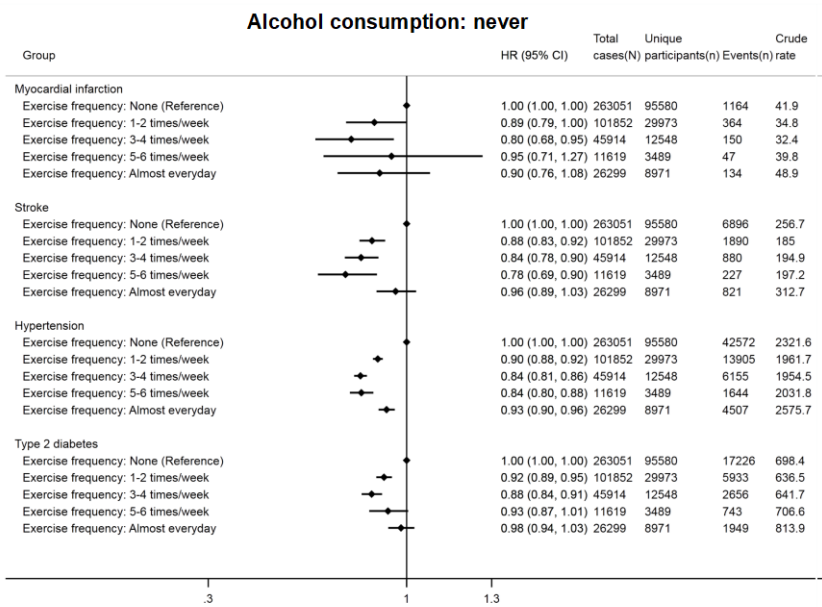


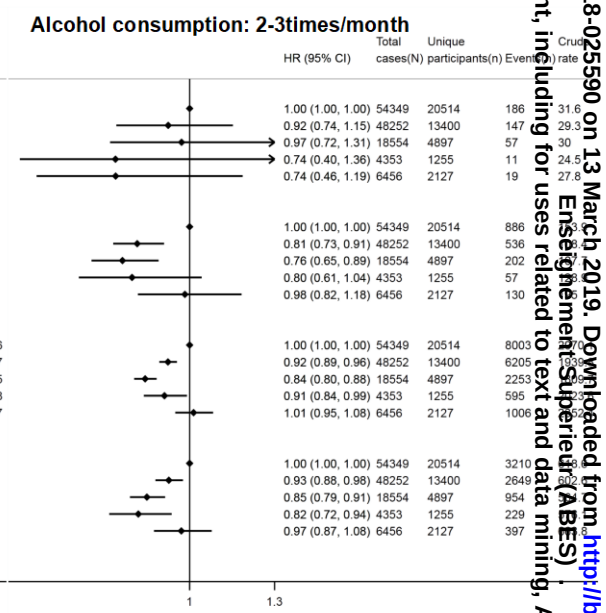
Supplementary Figure 3. Associations of exercise with incident myocardial infarction, stroke, hypertension and Type 2 diabetes (top panel) and various incident cancer outcomes (bottom panel) after excluding data from the first 2-year follow-up period. Note: Cox regression models using age as the underlying 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”

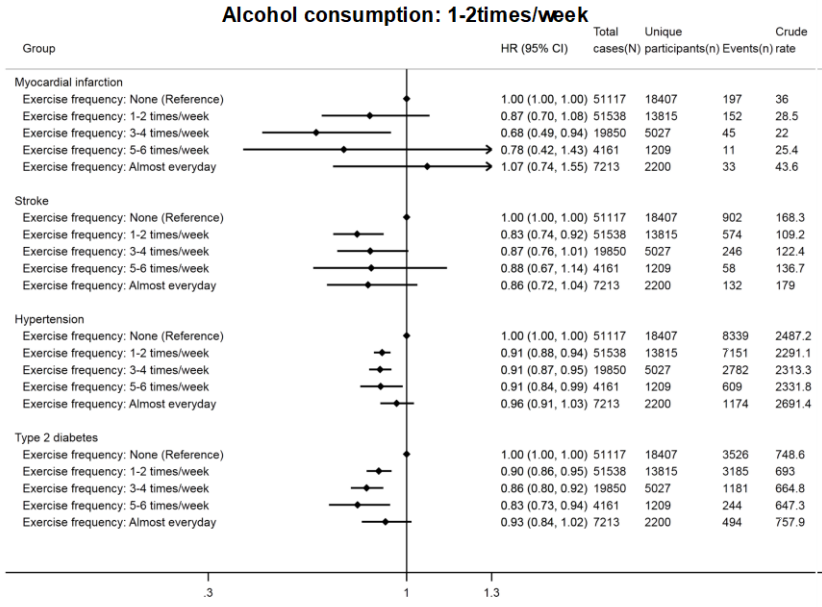
indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and “n” indicates numbers of unique participants at baseline. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

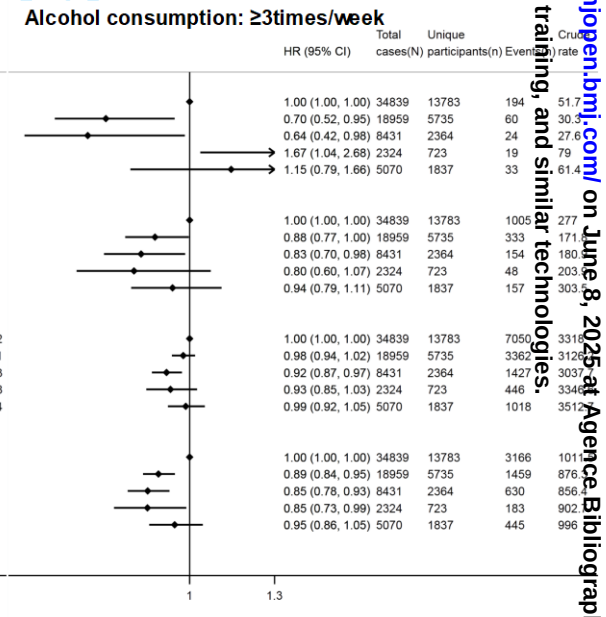


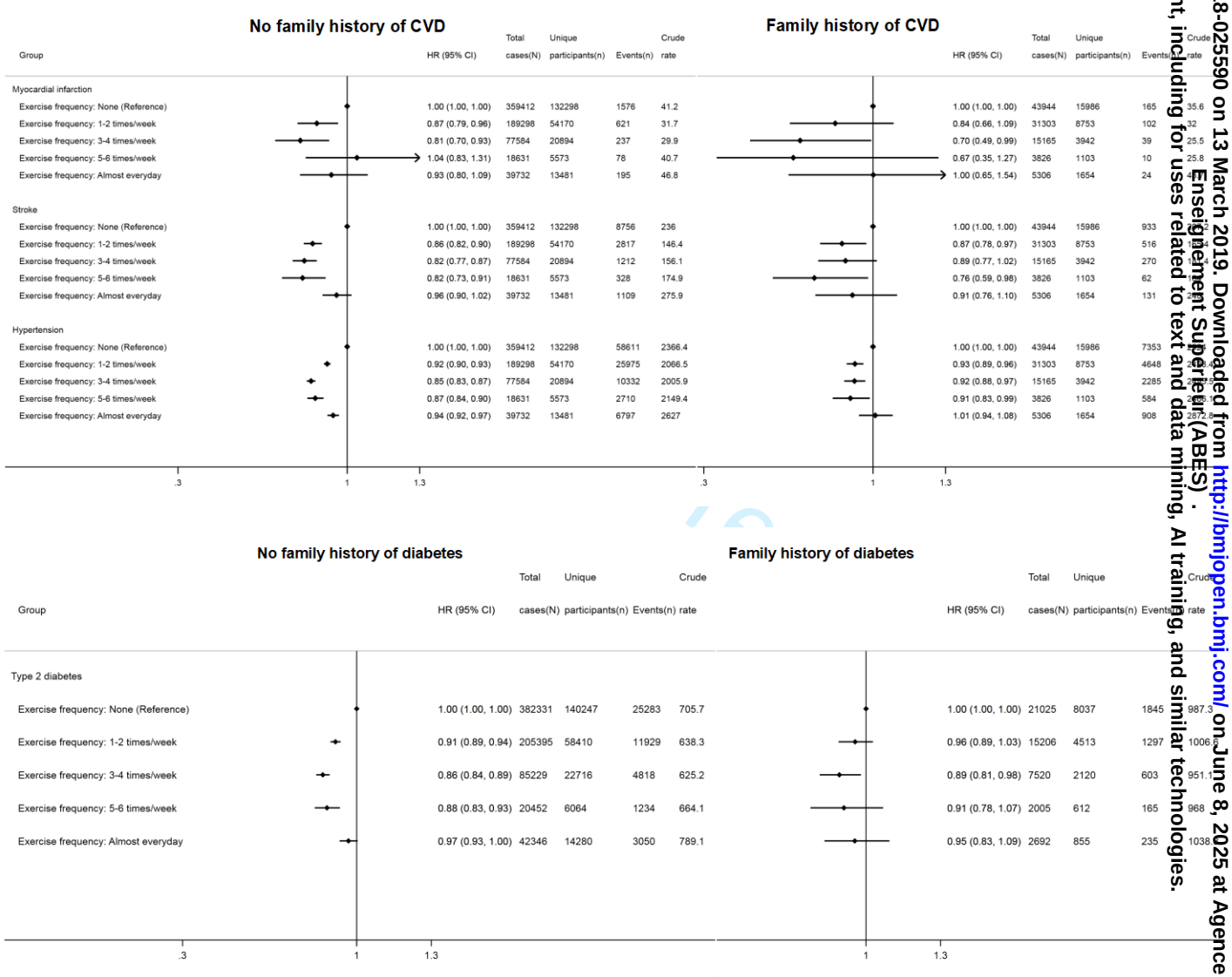


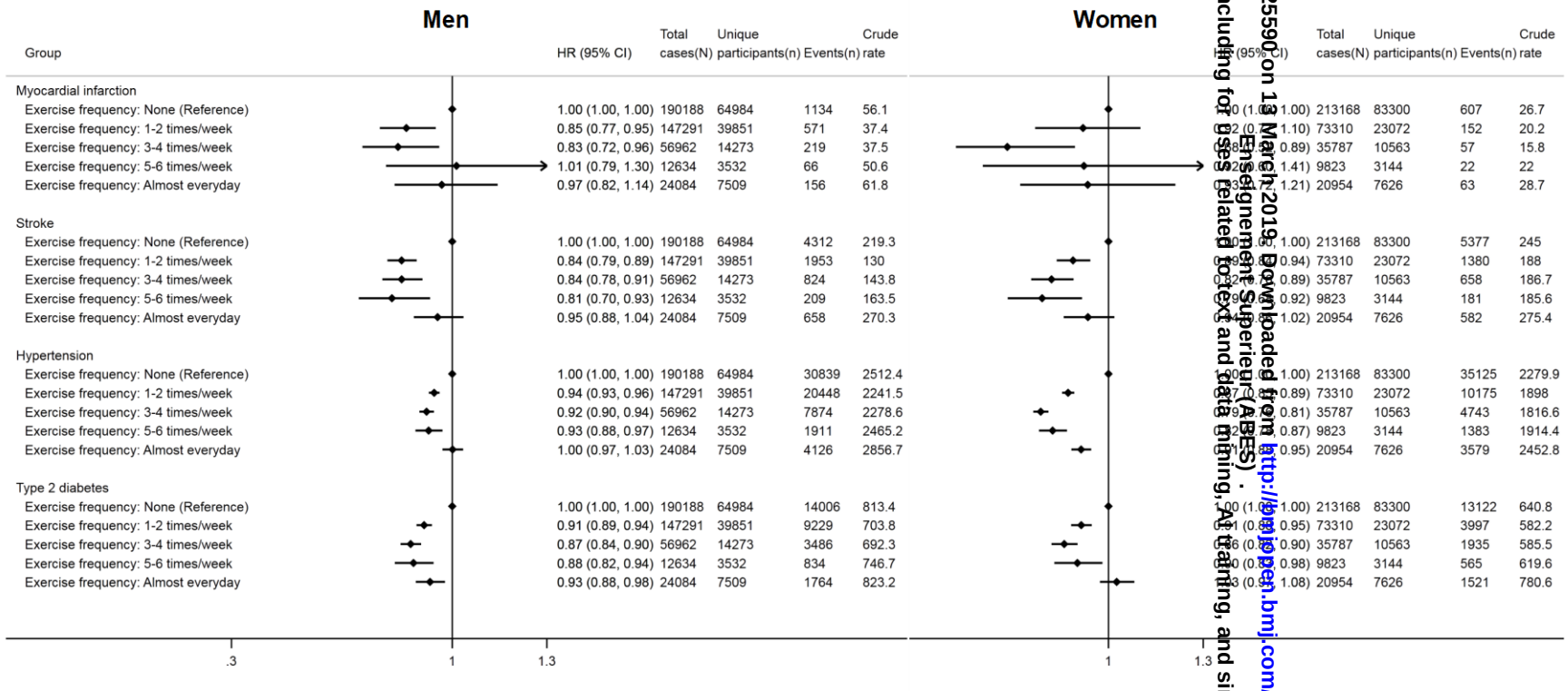






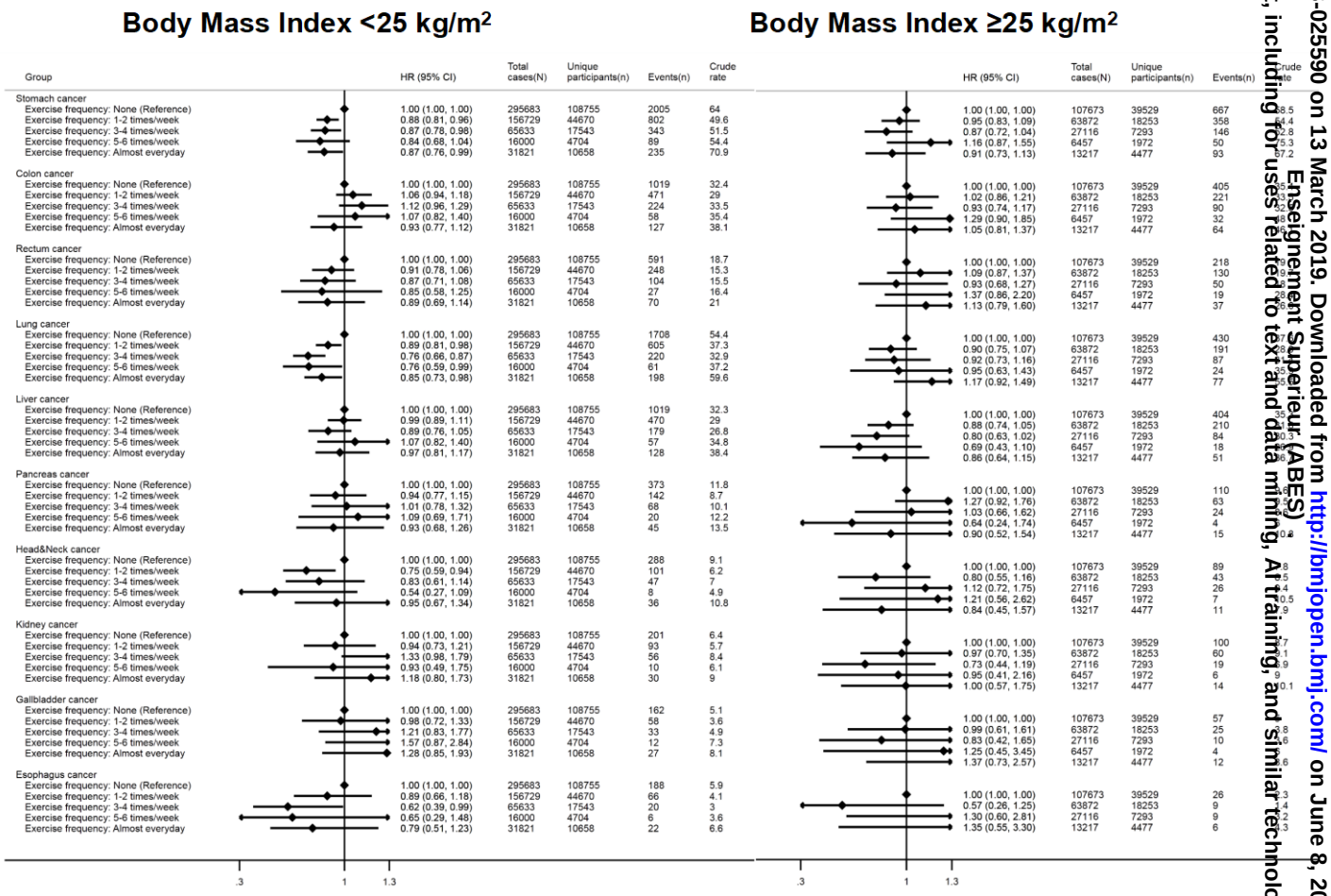


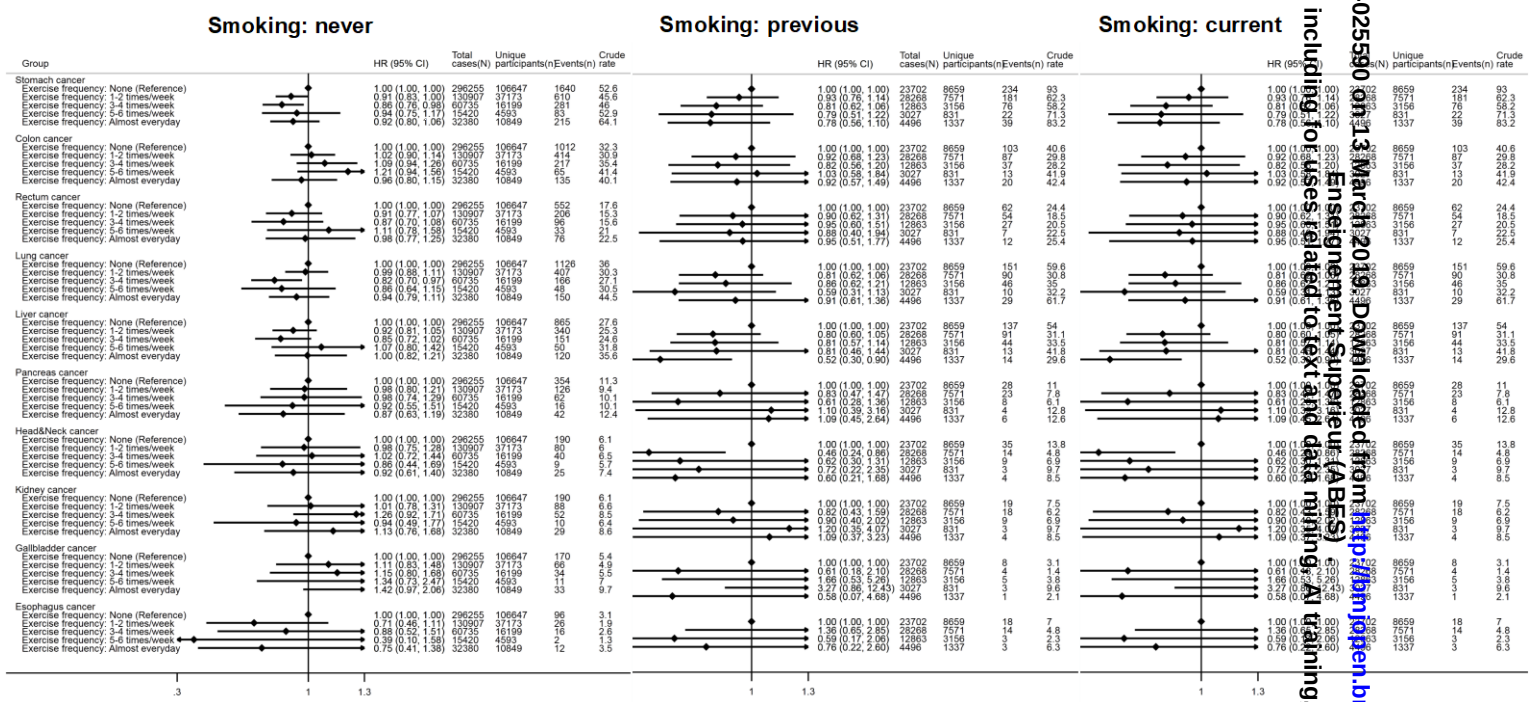


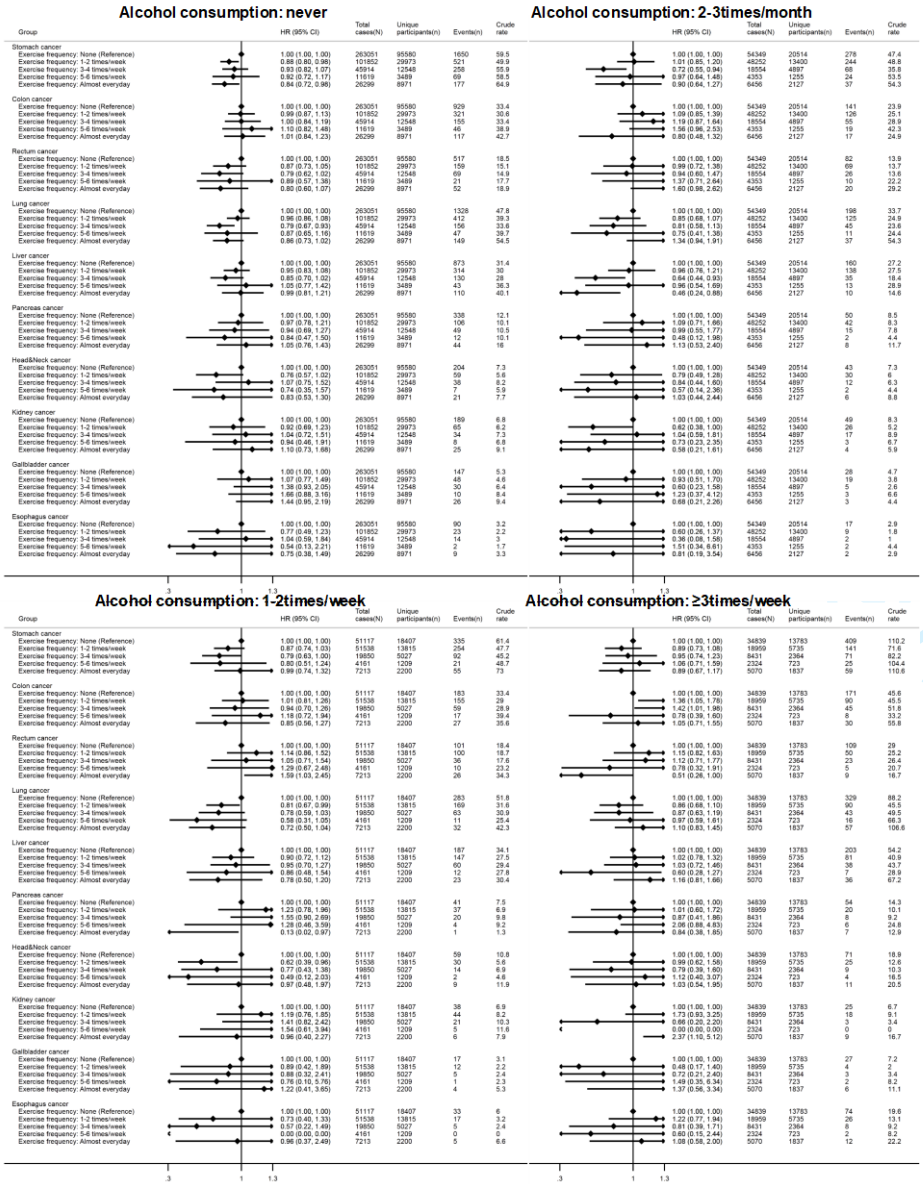


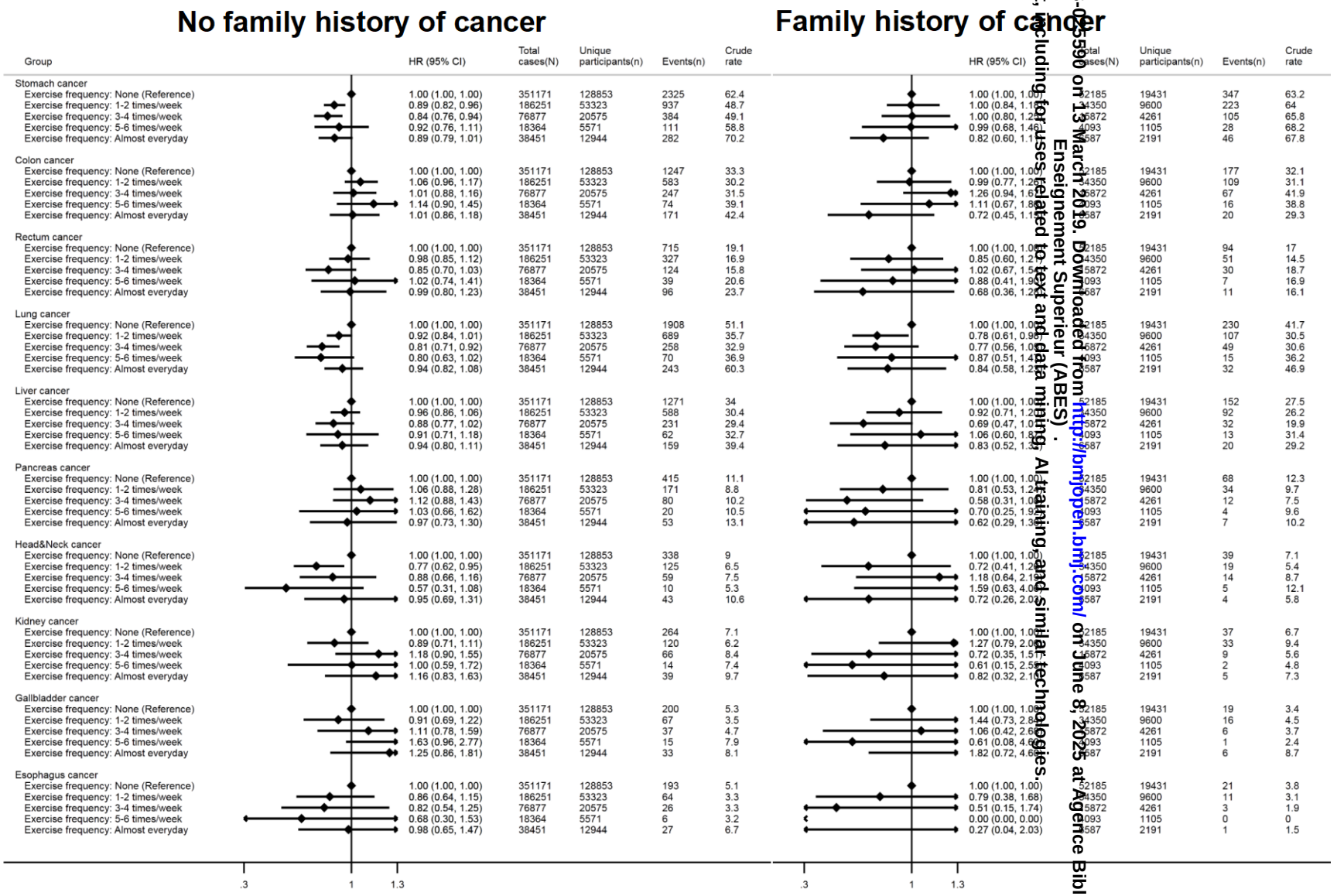
Supplementary Figure 4. Results from running Cox regression models examining effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequency and incident myocardial infarction, stroke, hypertension and type 2 diabetes. 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 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 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 – myocardial infarction (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;

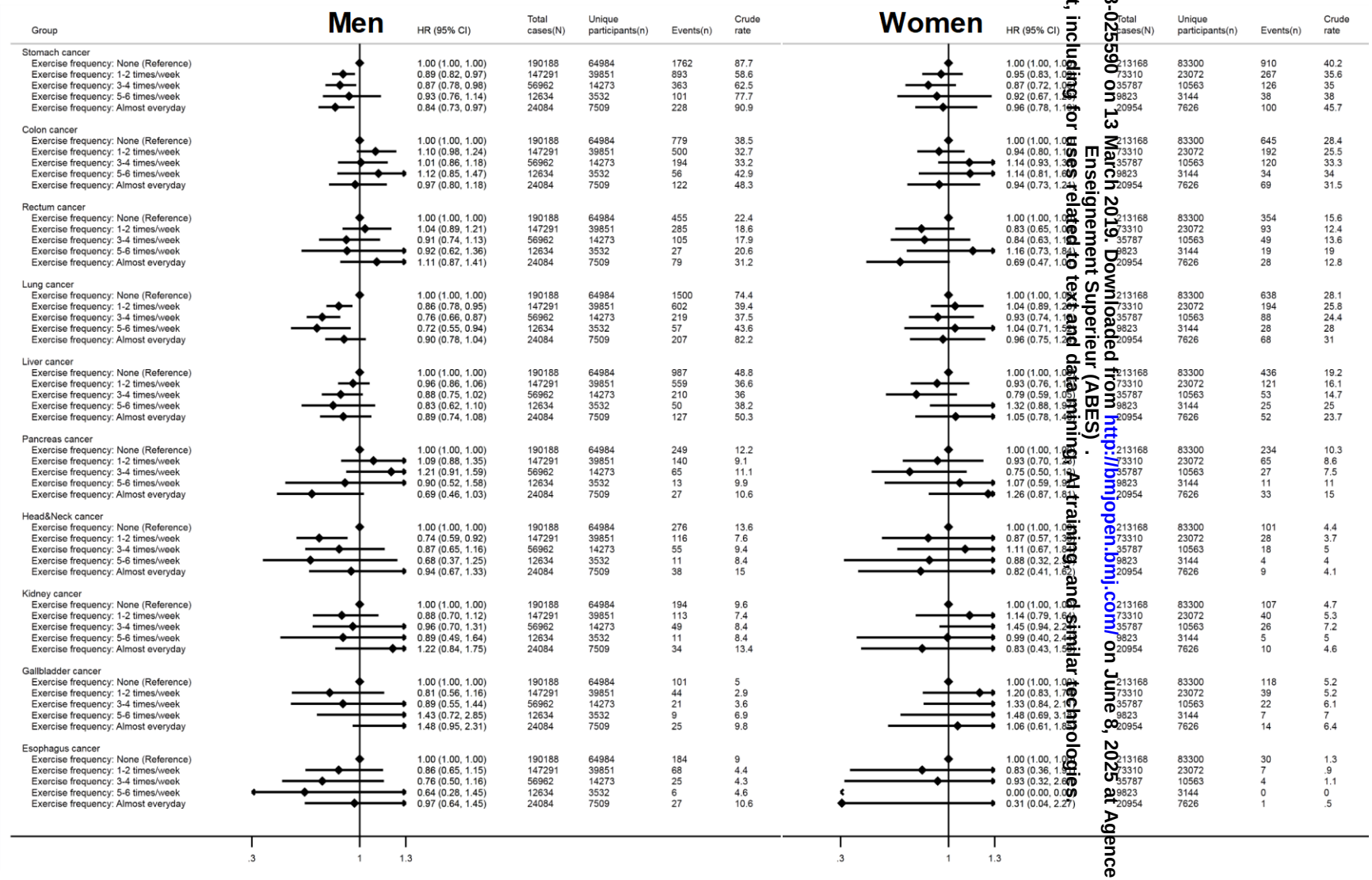
myocardial infarction (p-value = 0.643), stroke (p-value = 0.661), hypertension (p-value <0.001) and type 2 diabetes (p-value = 0.980) by smoking; myocardial infarction (p-value = 0.300), stroke (p-value = 0.607), hypertension (p-value <0.001) and type 2 diabetes (p-value = 0.081) by alcohol consumption; myocardial infarction (p-value = 0.590), stroke (p-value = 0.505) and hypertension (p-value = 0.029) by family history of cardiovascular disease; type 2 diabetes (p-value = 0.952) by family history of diabetes; and myocardial infarction (p-value = 0.334), stroke (p-value = 0.818), hypertension (p-value <0.001) and type 2 diabetes (p-value = 0.012) by sex.
Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals











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 frequency and various incident cancer outcomes. 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 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 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 terms – stomach cancer (p-value = 0.274), colon cancer (p-value = 0.940), rectum cancer (p-value = 0.107), lung cancer (p-value = 0.016), liver cancer (p-value = 0.129), pancreas cancer (p-value = 0.960), head & neck cancer (p-value = 0.488), kidney cancer (p-value = 0.285), gallbladder cancer (p-value = 0.970), and esophagus cancer (p-value = 0.263) by body mass index; stomach cancer (p-value = 0.699), colon cancer (p-value = 0.932), rectum cancer (p-value = 0.610), lung cancer (p-value = 0.492), liver cancer (p-value = 0.405), pancreas cancer (p-value = 0.338), head & neck cancer (p-value = 0.562), kidney cancer (p-value = 0.280), gallbladder cancer (p-value = 0.295), and esophagus cancer (p-value = 0.092) by smoking ; stomach cancer (p-value = 0.655), colon cancer (p-value = 0.977), rectum cancer (p-value = 0.433), lung cancer (p-value = 0.387), liver cancer (p-value = 0.704), pancreas cancer (p-value = 0.711), head & neck cancer (p-value = 1.000), kidney cancer (p-value = 0.336), gallbladder cancer (p-value = 0.350), and esophagus cancer (p-value = 0.550) by alcohol consumption ; stomach cancer (p-value = 0.996), colon cancer (p-value = 0.399), rectum cancer (p-value = 0.478), lung cancer (p-value = 0.007), liver cancer (p-value = 0.337), pancreas cancer (p-value = 0.086), head & neck cancer (p-value = 0.712), kidney cancer (p-value = 0.319), gallbladder cancer (p-value = 0.766), and esophagus cancer (p-value = 0.098) by family history of cancer; and stomach cancer (p-value = 0.405), colon cancer (p-value = 0.957), rectum cancer (p-value = 0.106), lung cancer (p-value = 0.063), liver cancer (p-value = 0.278), pancreas cancer (p-value = 0.265), head & neck cancer (p-value = 0.907), kidney cancer (p-value = 0.967), gallbladder cancer (p-value = 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 non-fatal 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.

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] diabetes[5] and cancer,[6] has increased dramatically over the past few decades, although age-standardised cardiovascular disease and cancer rates as well as systolic blood pressure levels[7] 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 diabetes[10] has increased more rapidly, while the age-standardised prevalence of cardiovascular disease[3]

and systolic blood pressure levels[7] 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 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, 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 levels[18] 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 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 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 out-patient 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' in-patient 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 ≥90 mm Hg) and fasting glucose levels (e.g., ≥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 (interquartile range: 10.2-11.3 years)

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, ≥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, ≥25kg^2/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 ≥140 mm Hg or diastolic ≥90 mm Hg), diabetes (additionally, fasting glucose levels ≥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

(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., ≥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

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 research[25-27] 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] diabetes[33-40] and different type of cancers.[41-47] 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,[48] and linear associations with the incidence of hypertension[49] 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 ≥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 hypertension[51-53] 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 ≥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.

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 in-patient 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 non-communicable diseases[12] 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

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 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 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) with the entire South

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 everyday (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)

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 adults (2002-2015) with the entire South Korean population’s health insurance system.

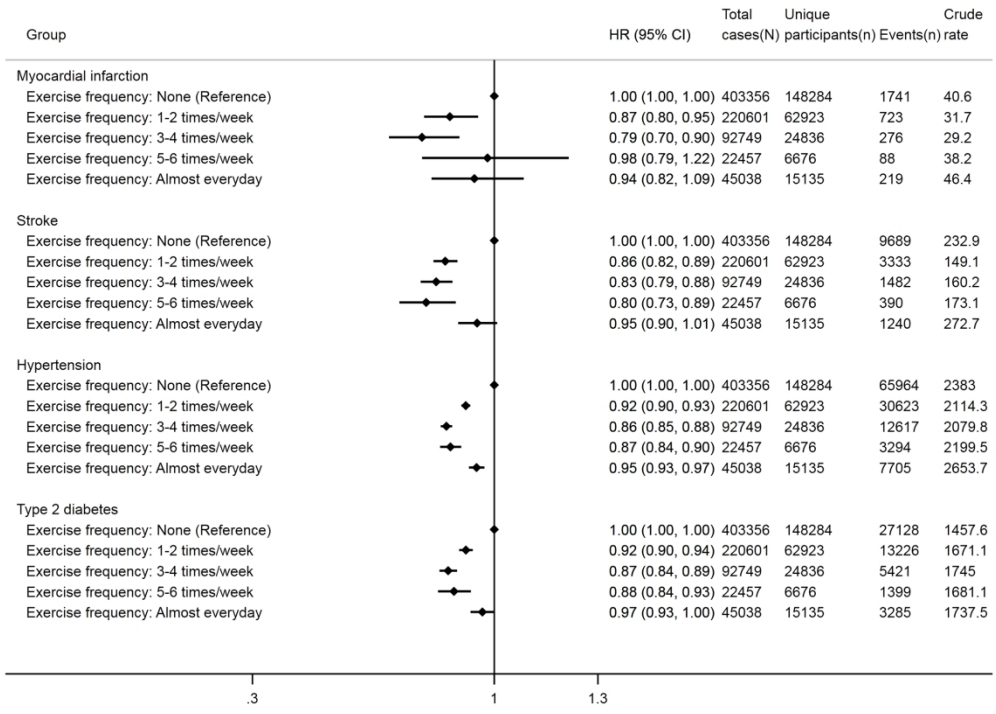

Figure 2. Associations of exercise frequency with various incident cardiovascular disease outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of heart disease, 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

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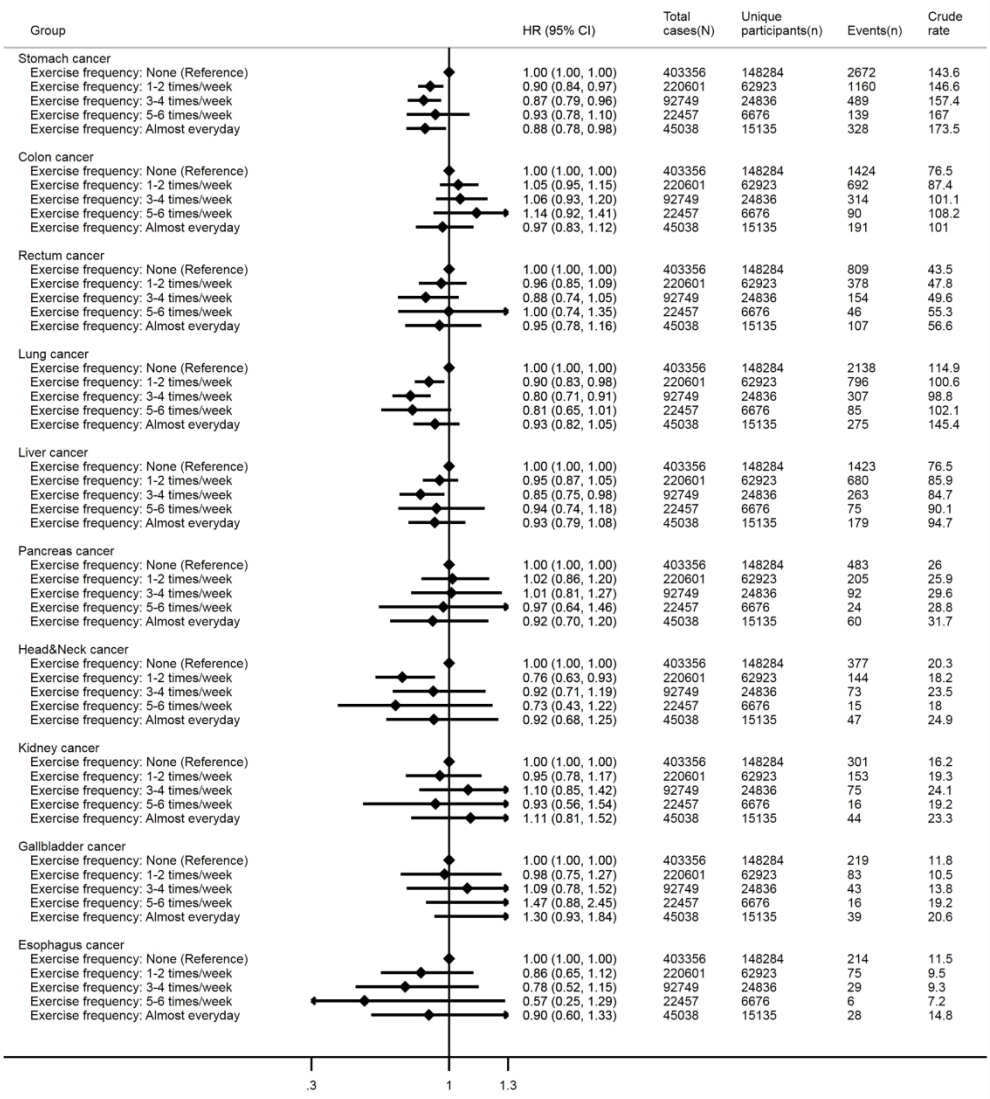

Figure 3. Associations of exercise frequency with various incident cancer outcomes. Cox regression models with age as the underlying timescale were adjusted for sex, body mass index, systolic blood pressure, fasting glucose levels, total cholesterol levels, family history of cancer, smoking status and 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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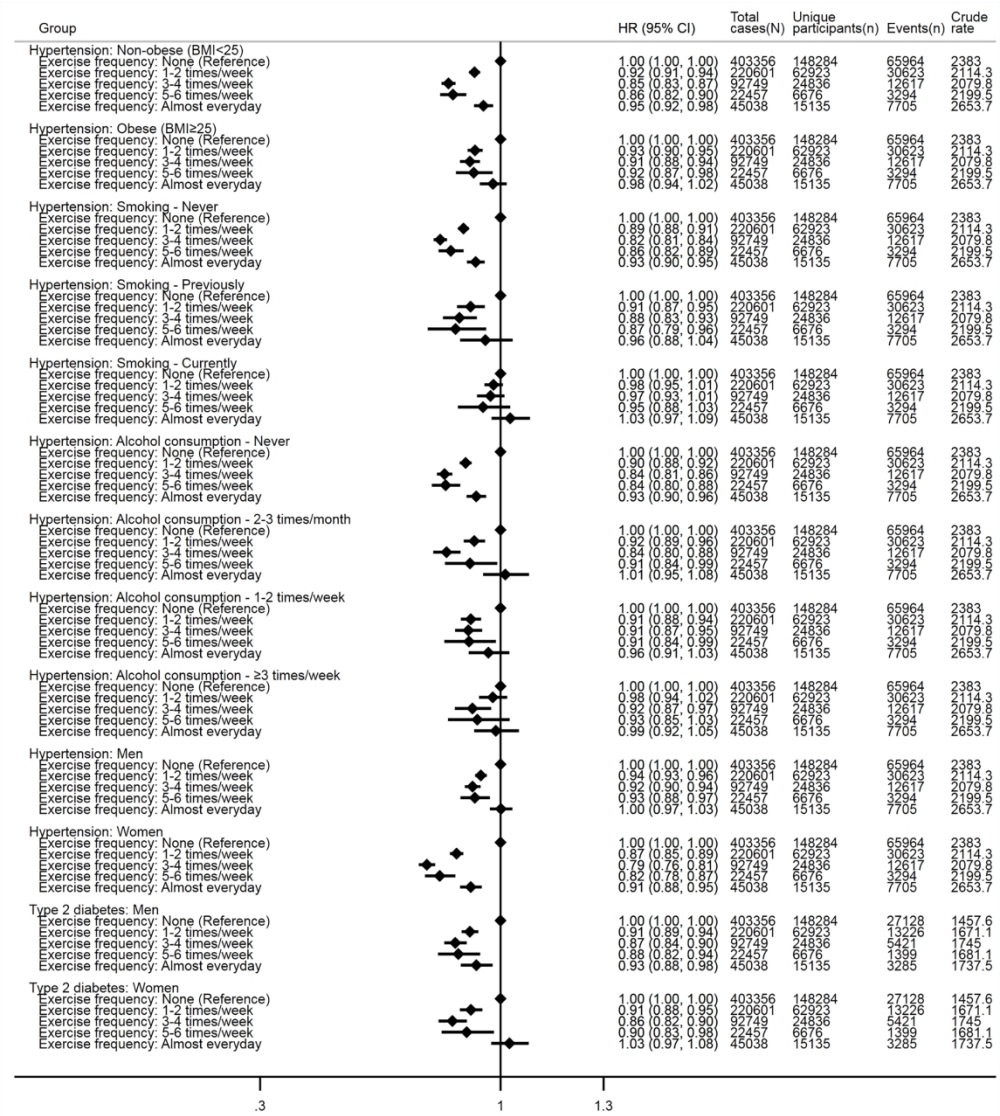


Figure 4. Results from assessment of effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequency and each incident disease outcome. Only associations for which the multiplicative interaction terms were statistically 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

Supplementary Table 1. Definitions for classification of incident disease outcomes

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

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

Repeat visit 1st	Variables	All (n=215,295)	Exercise frequency				
			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, 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	120.5 (14.4)	120.6 (14.7)	120.4 (13.9)	120.0 (13.8)	119.6 (13.9)	121.4 (14.6)
	Diastolic blood pressure, mm Hg	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 (35.8)	197.4 (35.9)	197.8 (36.7)
	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%

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

Repeat visit 2nd	Variables	All (n=150,845)	Exercise frequency				
			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, kg^2/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, mm Hg	120.9 (14.1)	121.0 (14.5)	120.7 (13.7)	120.4 (13.6)	120.3 (13.7)	122.0 (14.5)
	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)	76.0 (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 (36.5)
	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 3rd	Variables	All (n=80,639)	Exercise frequency				
			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, kg^2/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, mm Hg	121.1 (13.6)	120.9 (13.9)	120.9 (13.4)	121.0 (13.6)	120.6 (13.3)	122.0 (14.0)
	Diastolic blood pressure, mm Hg	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 (34.8)	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%

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

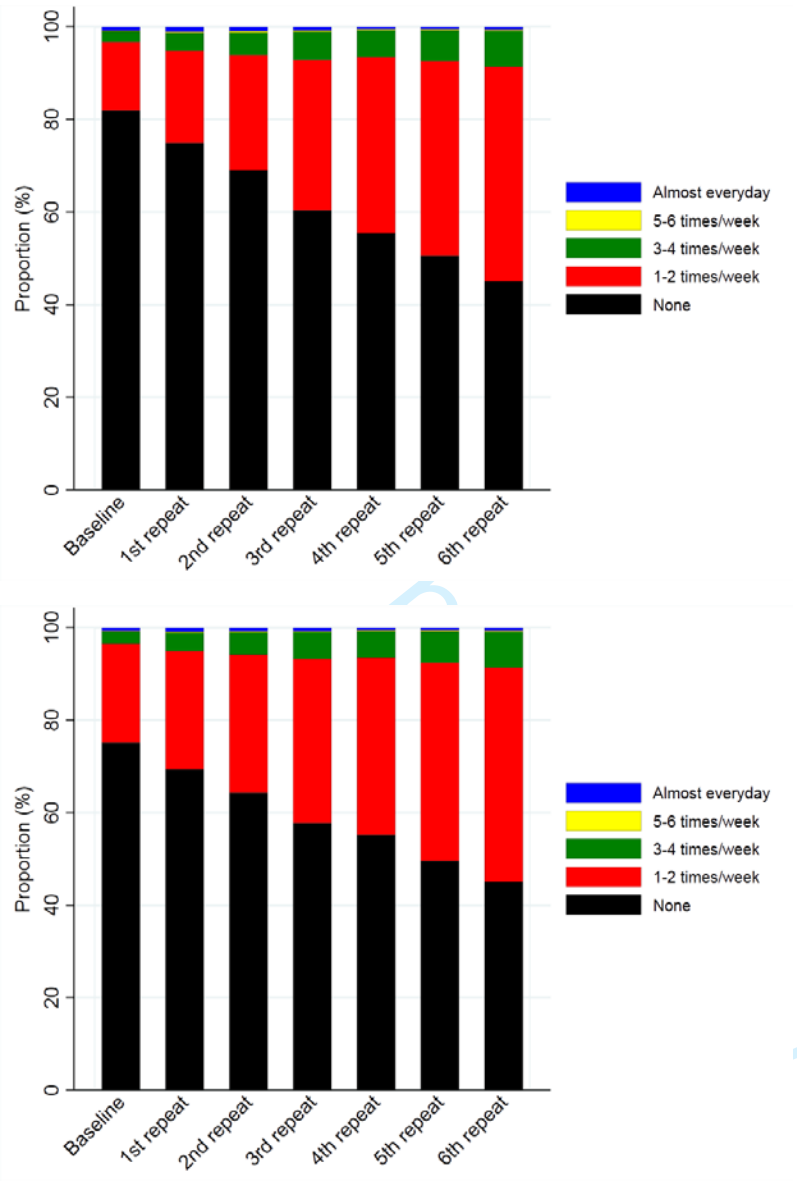
Repeat visit 4th	Variables	All (n=40,910)	Exercise frequency				
			None (n=17,678)	1-2 times/week (n=14,624)	3-4 times/week (n= 5,685)	5-6 times/week (n=1,094)	Almost everyday (n=1,829)
	Sex, %						
	Men	72.3%	61.6%	81.1%	81.5%	78.2%	73.9%
	Women	27.7%	38.4%	18.9%	18.5%	21.9%	26.1%
	Age, years	50.9 (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, kg^2/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, mm Hg	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, mm Hg	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 (34.8)	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%

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

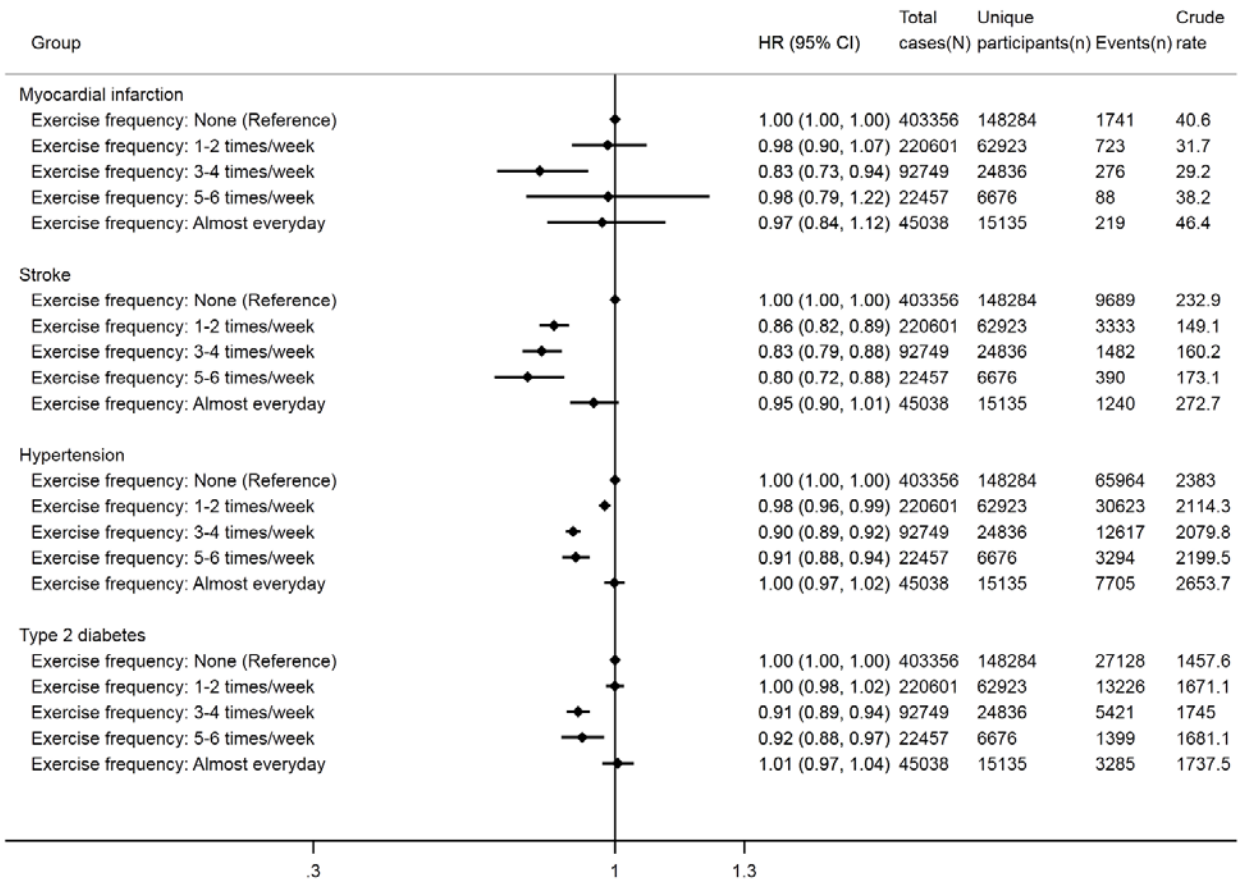
Repeat visit 5th	Variables	All (n= 26,356)	Exercise frequency				
			None (n=10,771)	1-2 times/week (n=9,807)	3-4 times/week (n=3,884)	5-6 times/week (n=724)	Almost everyday (n=1,170)
	Sex, %						
	Men	73.7%	62.6%	81.6%	82.4%	81.2%	76.9%
	Women	26.3%	37.4%	18.4%	17.6%	18.8%	23.0%
	Age, years	51.1 (4.9)	51.4 (5.1)	50.8 (4.7)	51.0 (4.7)	51.4 (5.0)	52.1 (5.6)
	Body Mass Index, kg^2/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, mm Hg	121.4 (13.0)	121.0 (13.4)	121.8 (12.9)	121.6 (12.8)	120.8 (12.9)	121.5 (12.7)
	Diastolic blood pressure, mm Hg	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 (37.0)
	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%

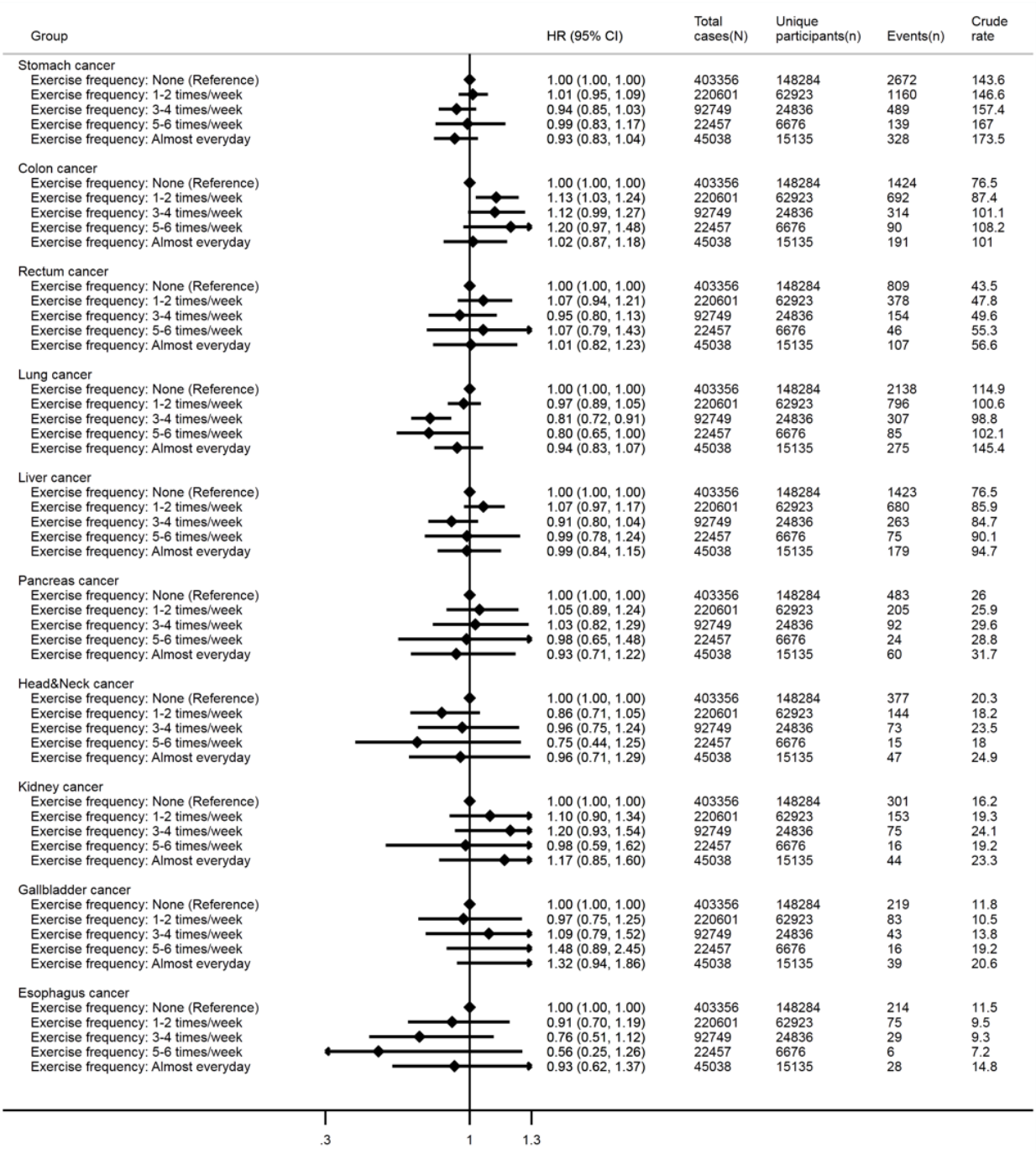
Supplementary Table 2. Participants' characteristics at 1st, 2nd, 3rd, 4th, 5th and 6th repeat-visit (cont.)

Repeat visit 6th	Variables	All (n= 12,302)	Exercise frequency				
			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, 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 (2.5)
	Systolic blood pressure, mm Hg	121.5 (12.8)	121.2 (13.0)	121.6 (12.6)	121.7 (12.8)	121.0 (12.5)	122.1 (12.3)
	Diastolic blood pressure, mm Hg	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 (34.3)
	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%

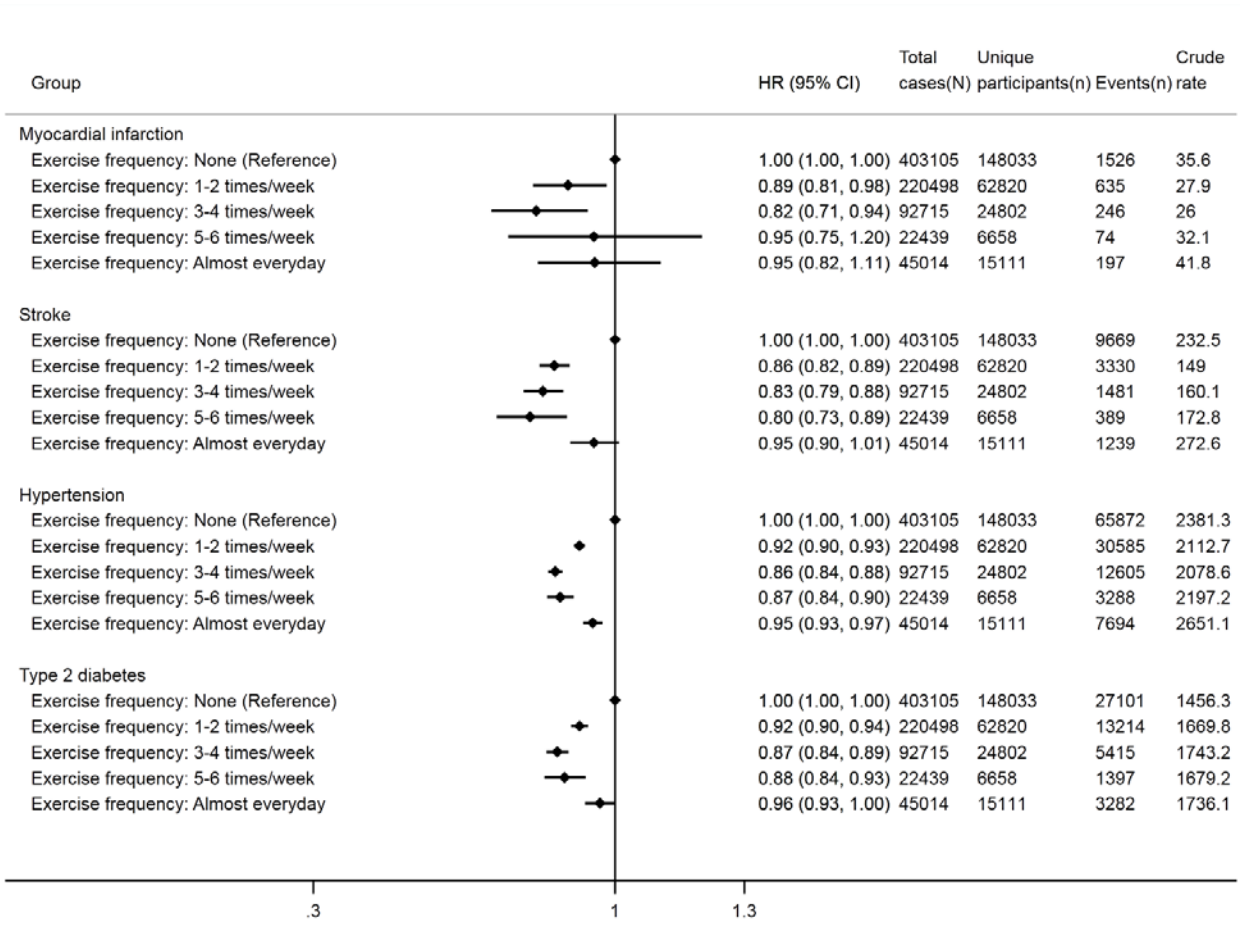


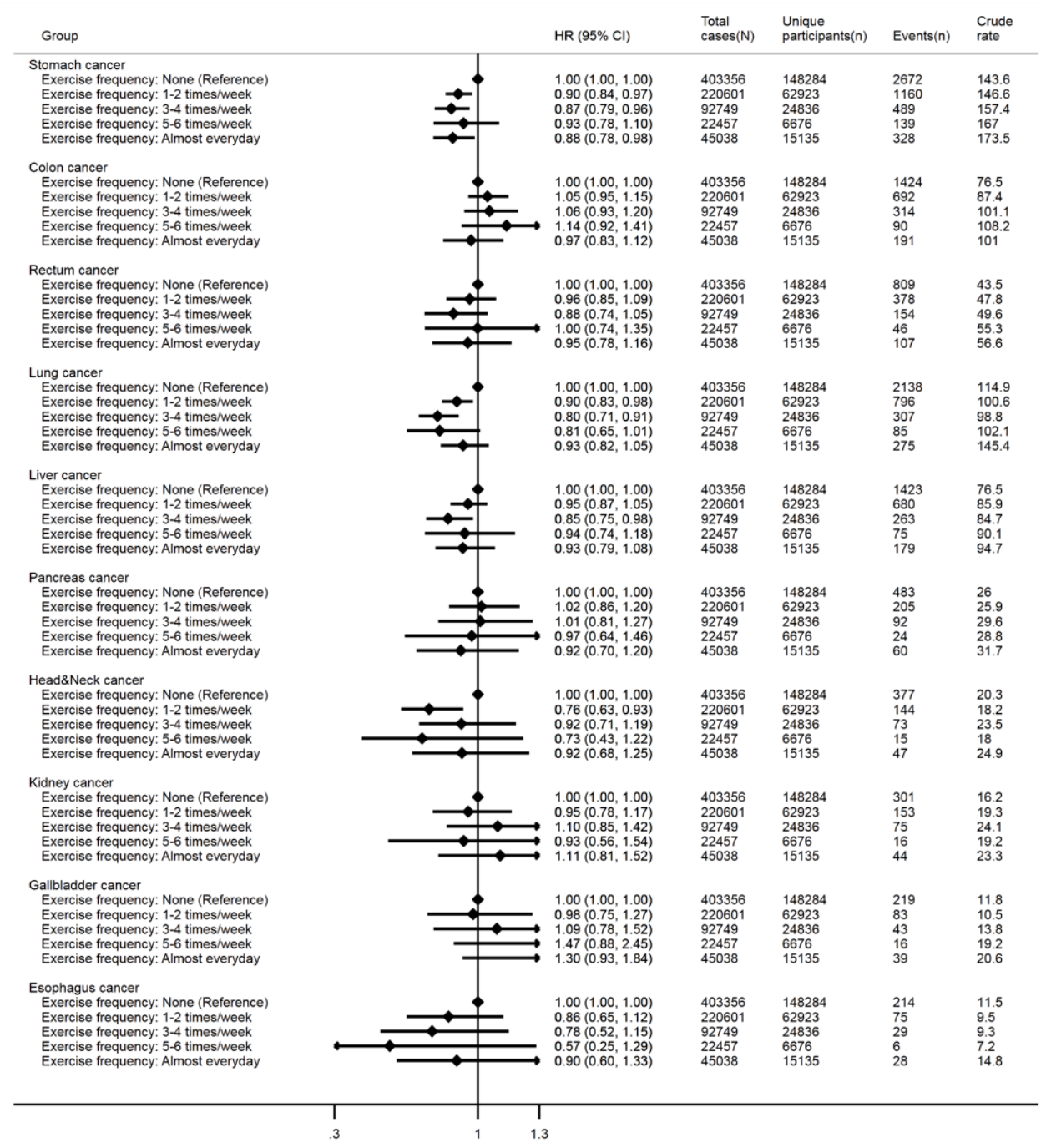
Supplementary Figure 1. Changes in proportions of exercise frequency categories across 7 time points in all 257,854 individuals who provided data at each respective assessment visit (top panel), and 12,302 individuals who provided data from all 7 assessment visits (bottom panel).





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

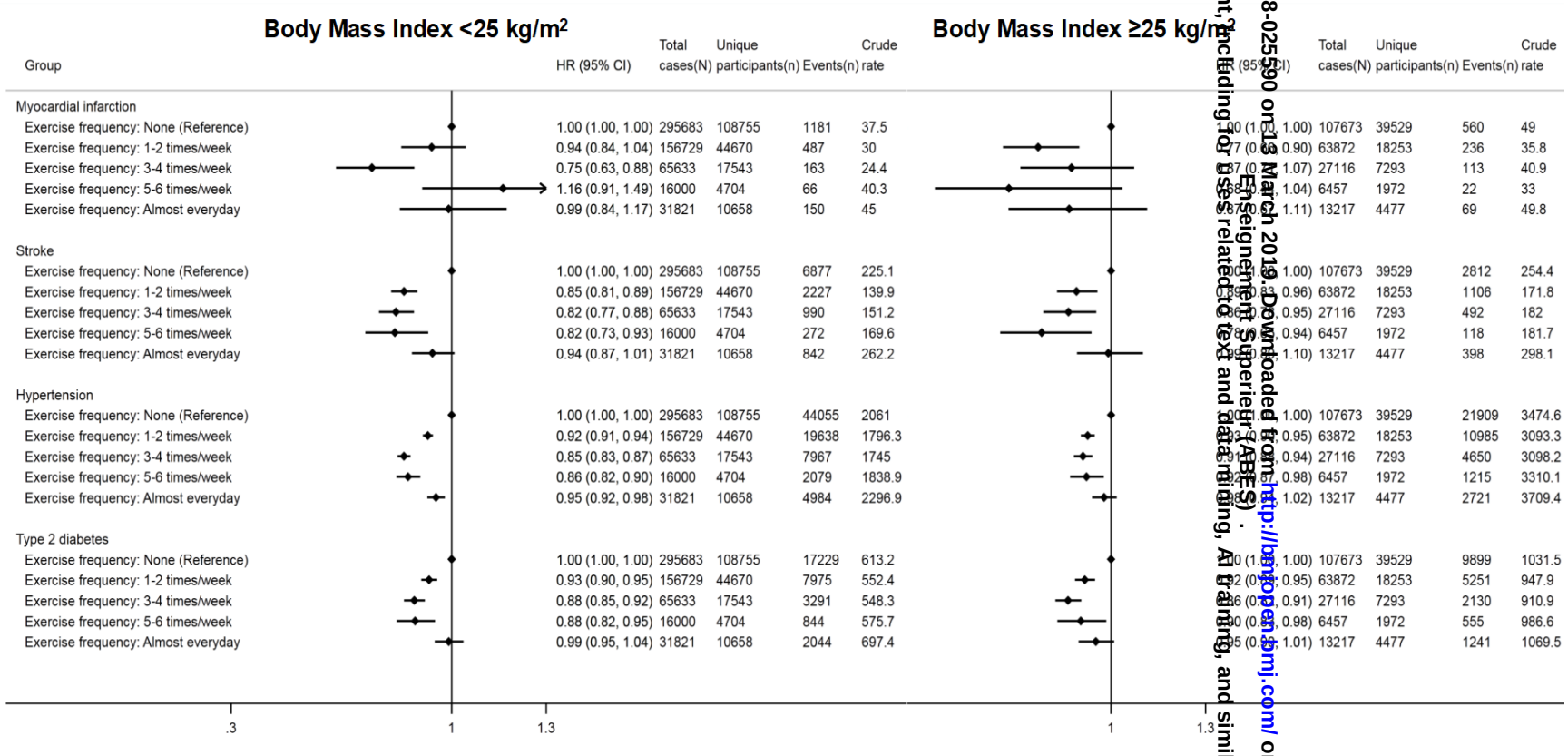


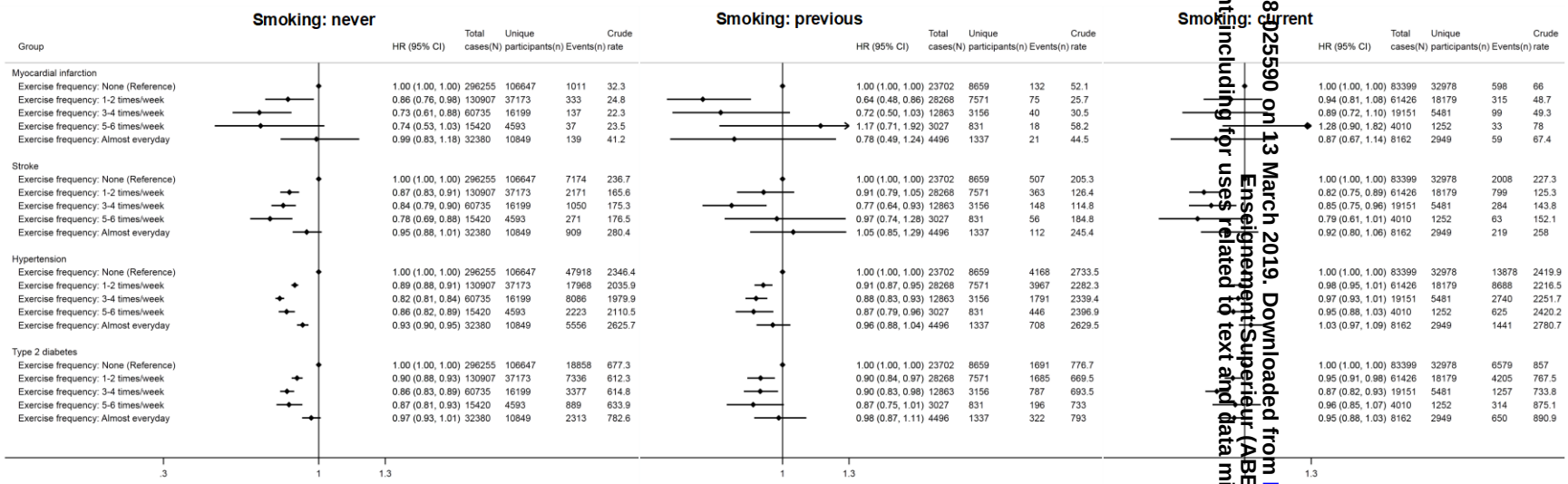


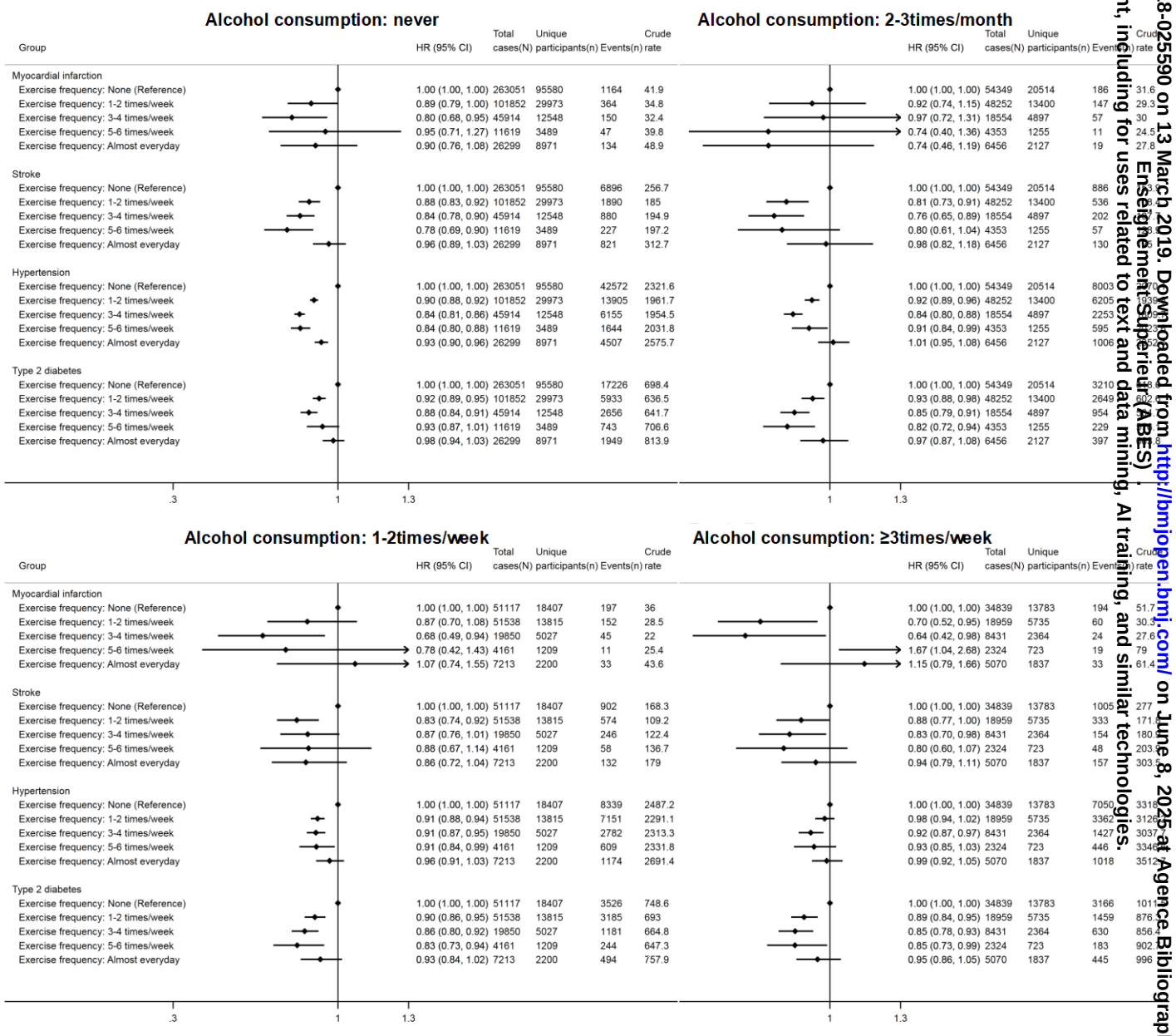
Group	HR (95% CI)	Total cases(N)	Unique participants(n)	Events(n)	Crude rate
Stomach cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	2672	143.6
Exercise frequency: 1-2 times/week	0.90 (0.84, 0.97)	220601	62923	1160	146.6
Exercise frequency: 3-4 times/week	0.87 (0.79, 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)	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
Lung cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	2138	114.9
Exercise frequency: 1-2 times/week	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
Liver 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					
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	24836	92	29.6
Exercise frequency: 5-6 times/week	0.97 (0.64, 1.46)	22457	6676	24	28.8
Exercise frequency: Almost everyday	0.92 (0.70, 1.20)	45038	15135	60	31.7
Head&Neck cancer					
Exercise frequency: None (Reference)	1.00 (1.00, 1.00)	403356	148284	377	20.3
Exercise frequency: 1-2 times/week	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	0.93 (0.56, 1.54)	22457	6676	16	19.2
Exercise frequency: Almost everyday	1.11 (0.81, 1.52)	45038	15135	44	23.3
Gallbladder 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
Esophagus cancer					
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	0.57 (0.25, 1.29)	22457	6676	6	7.2
Exercise frequency: Almost everyday	0.90 (0.60, 1.33)	45038	15135	28	14.8

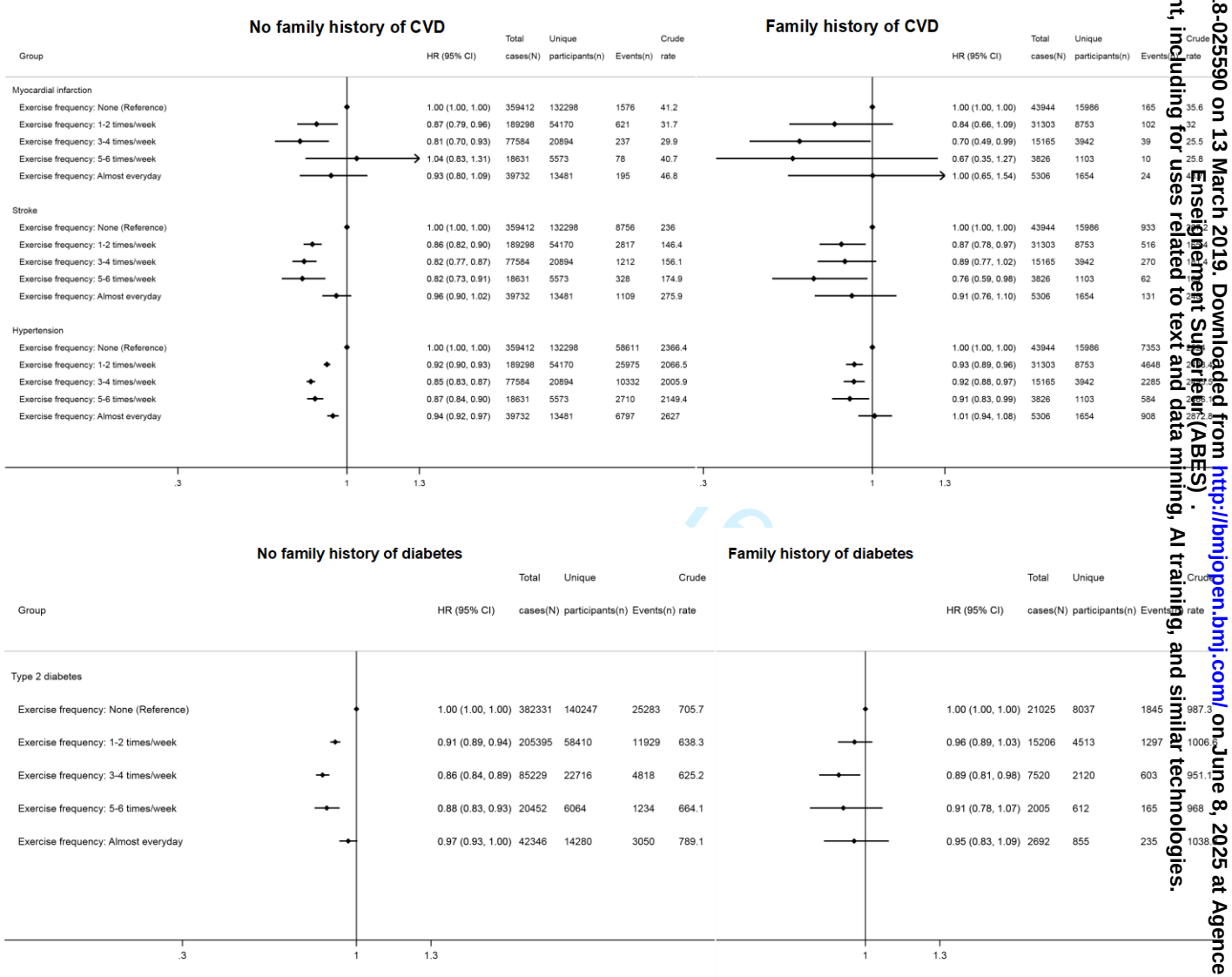
Supplementary Figure 3. Associations of exercise with incident myocardial infarction, stroke, hypertension and Type 2 diabetes (top panel) and various incident cancer outcomes (bottom panel) after excluding data from the first 2-year follow-up period. Note: Cox regression models using age as the underlying 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"

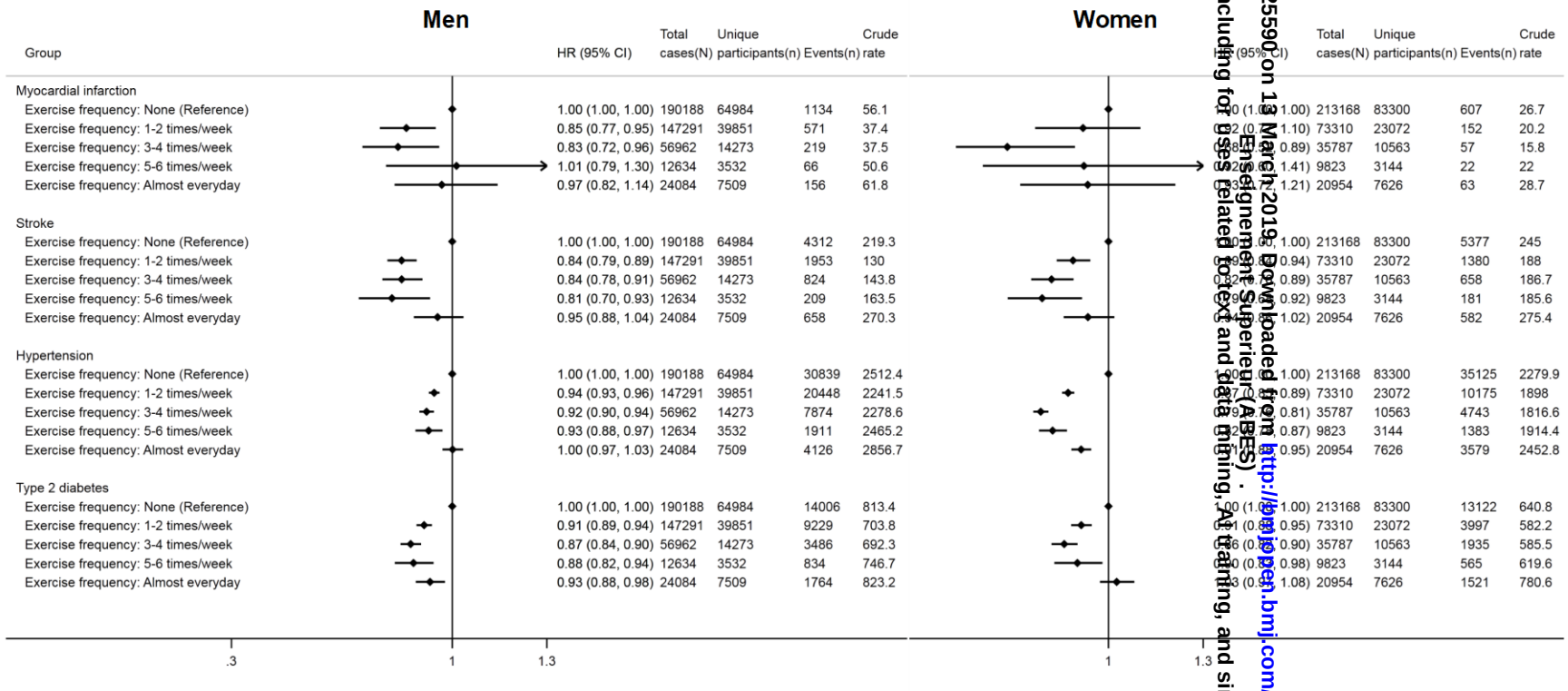
indicates numbers of total observations (i.e. participants who provided repeated measures are treated as separate observations) and “n” indicates numbers of unique participants at baseline.
Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals





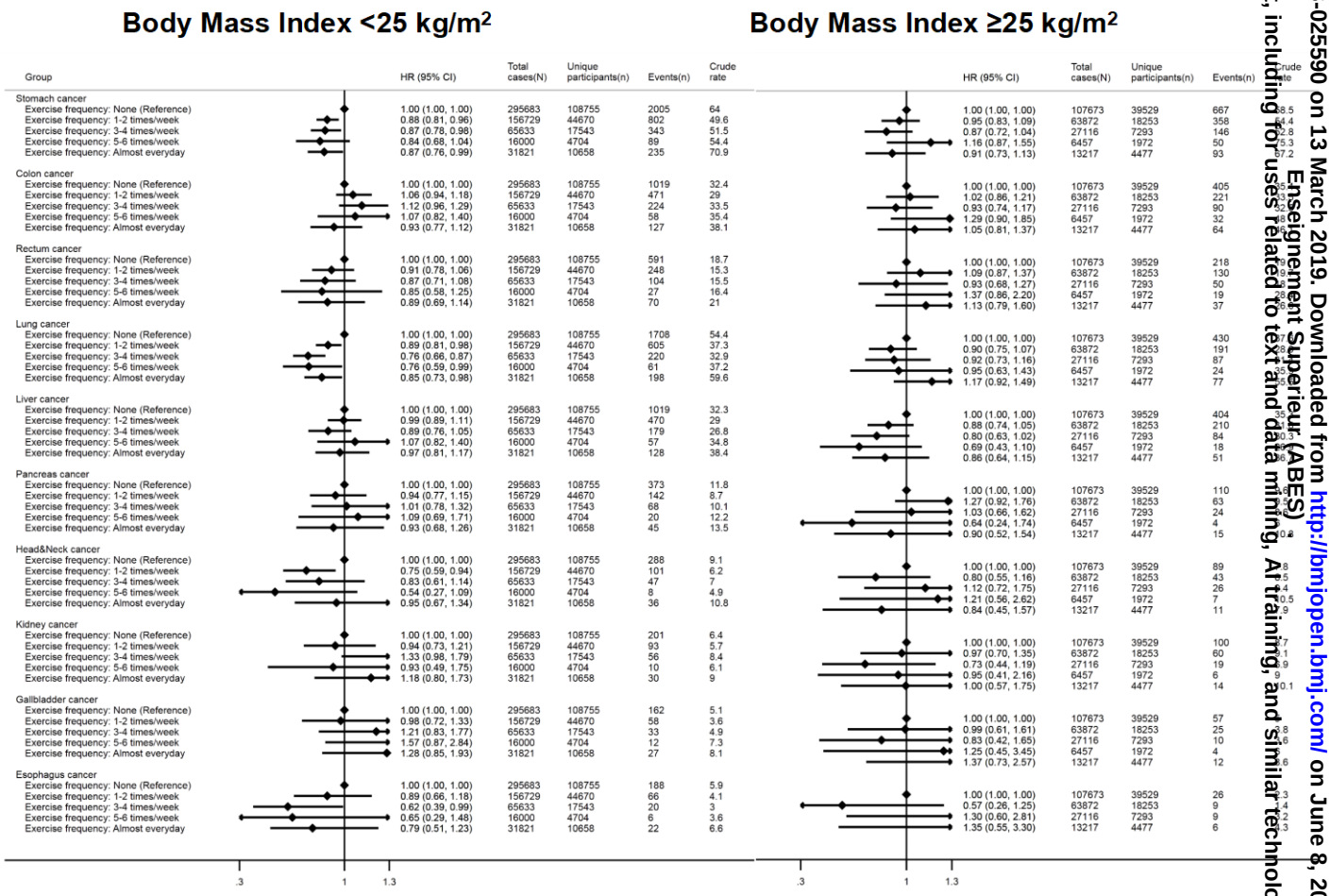


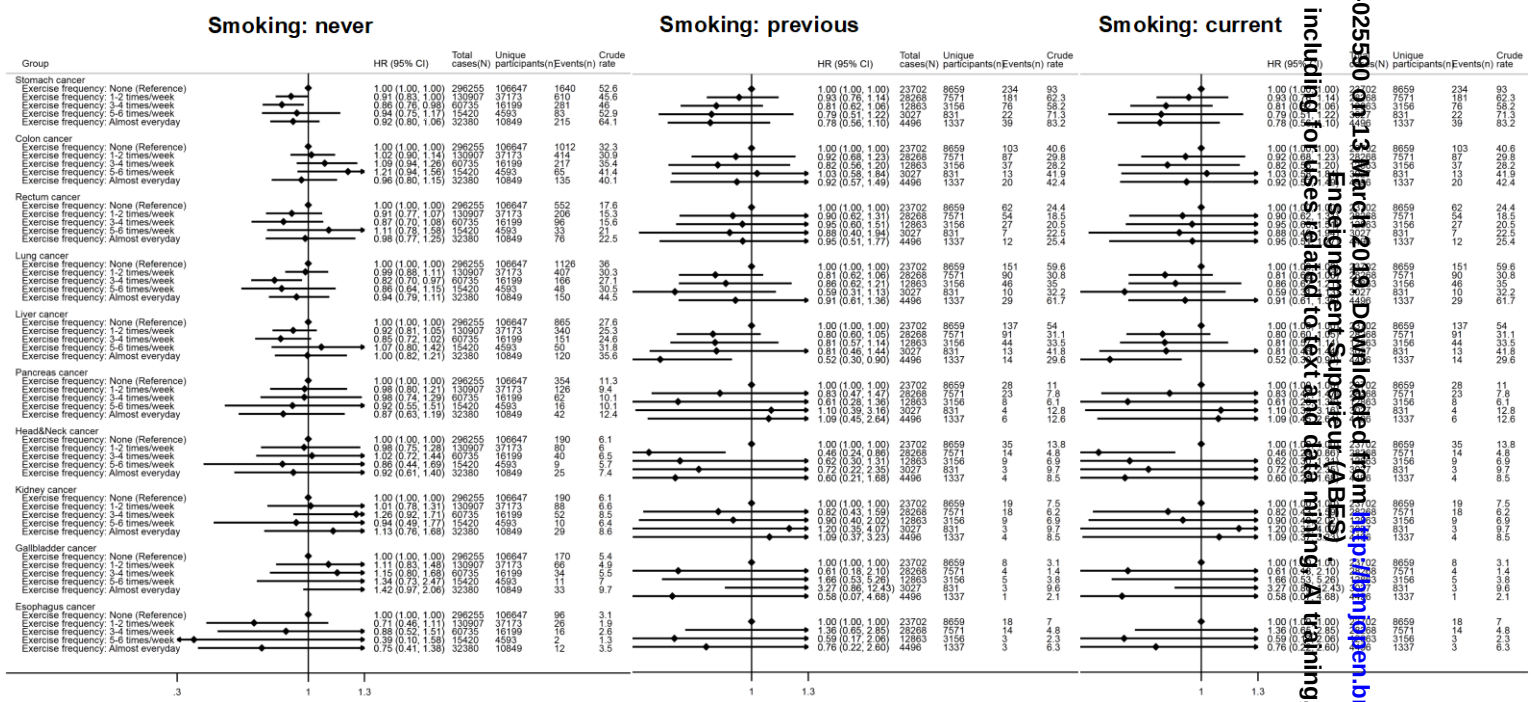


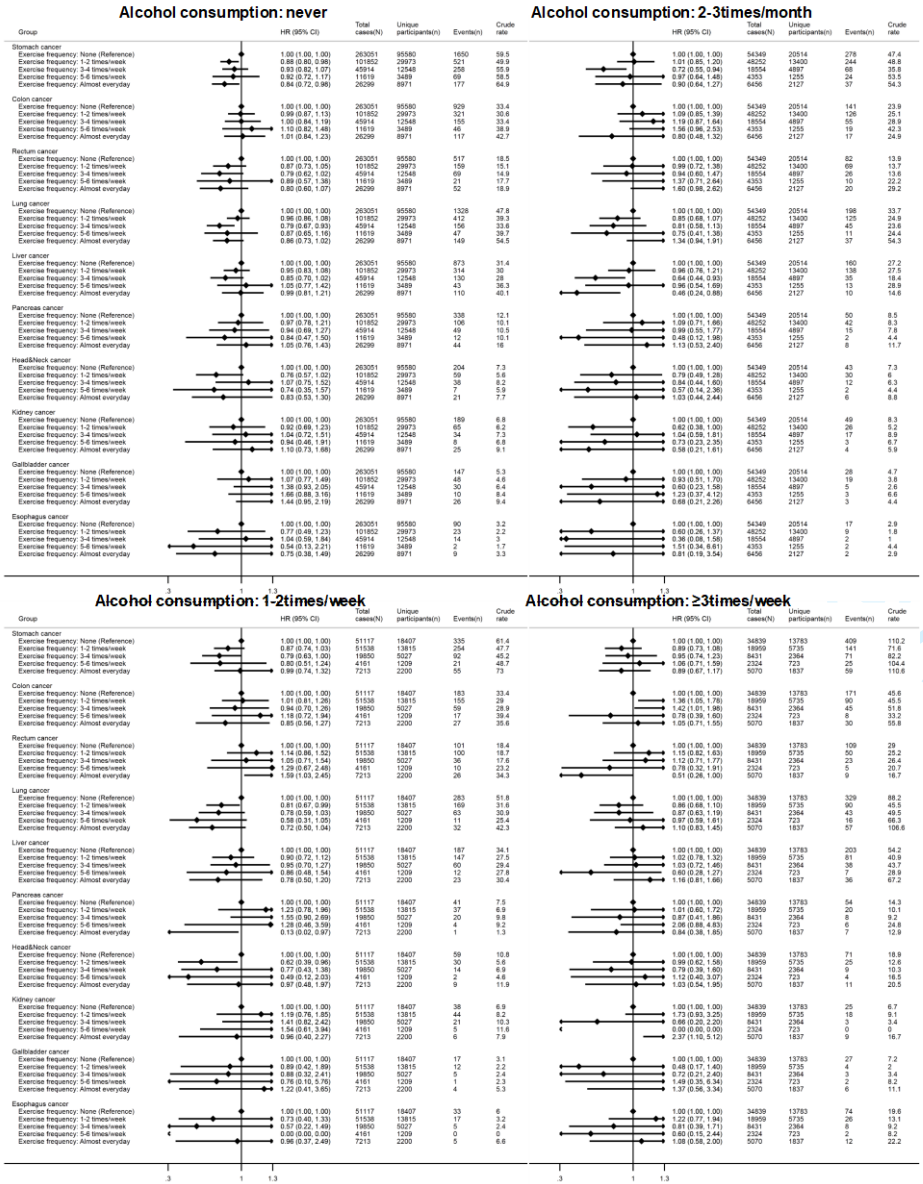


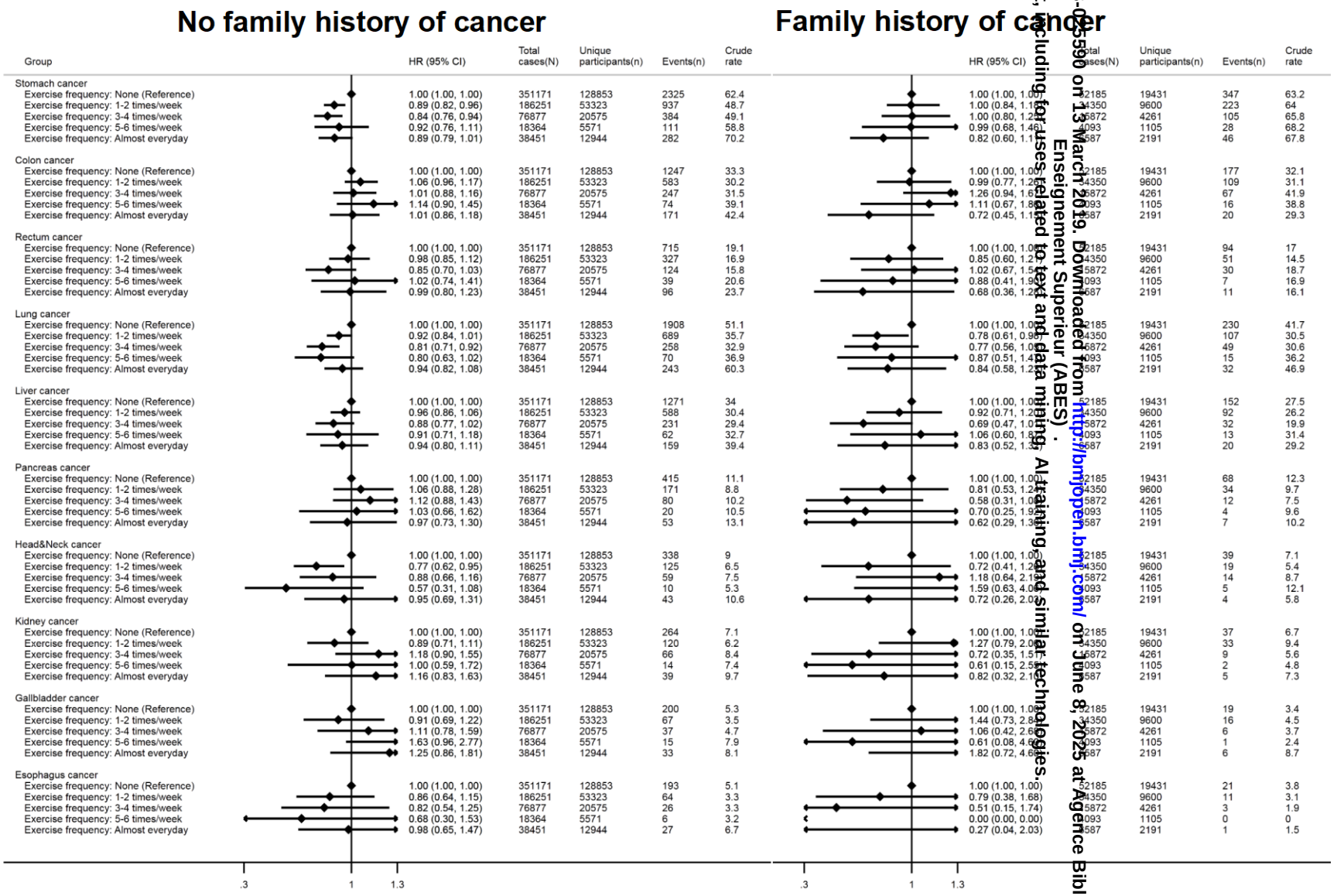
Supplementary Figure 4. Results from running Cox regression models examining effect modification of sex, body mass index, smoking, alcohol consumption, and family history of disease in the associations between exercise frequency and incident myocardial infarction, stroke, hypertension and type 2 diabetes. 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 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 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 – myocardial infarction (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;

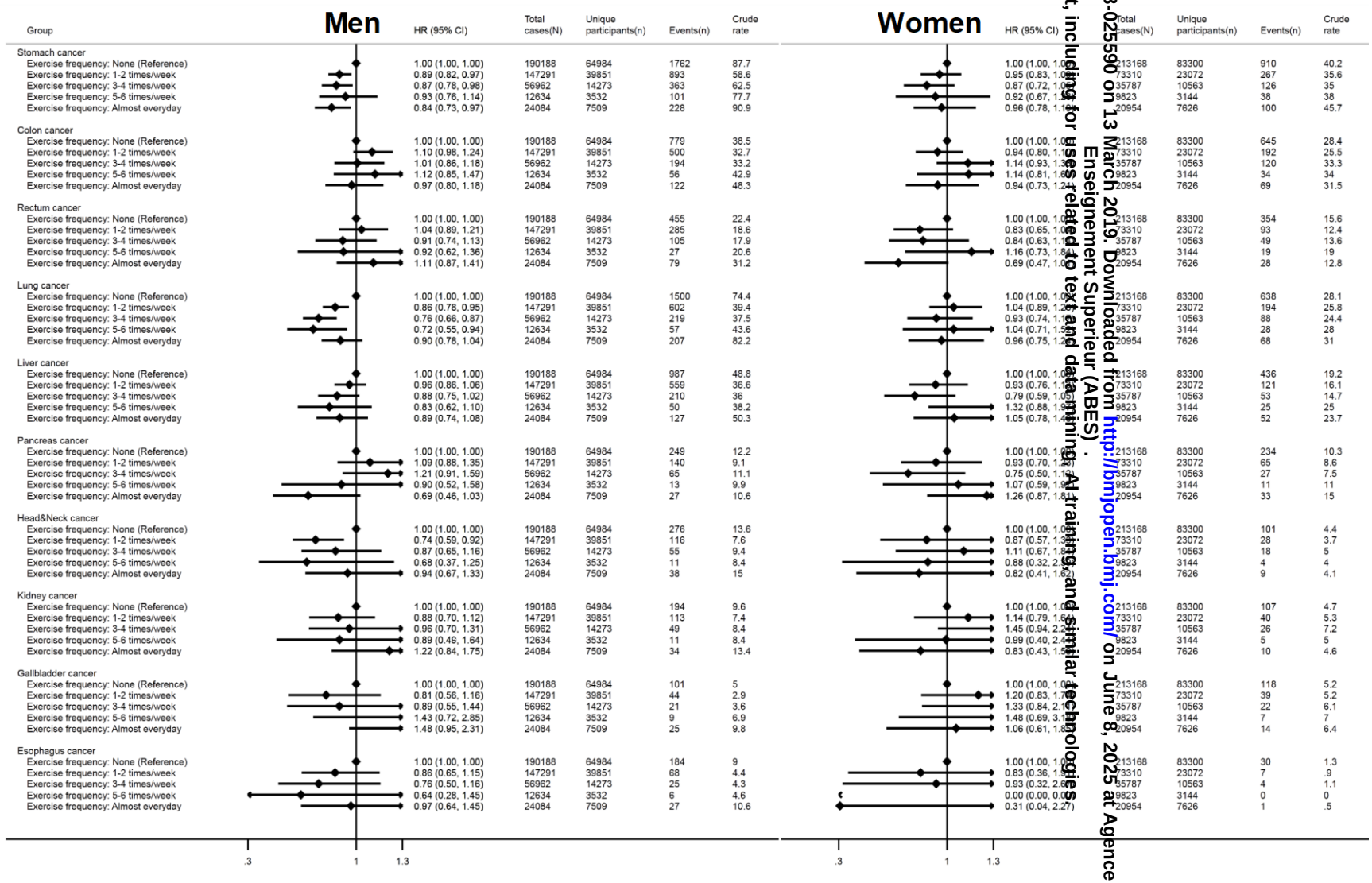
myocardial infarction (p-value = 0.643), stroke (p-value = 0.661), hypertension (p-value <0.001) and type 2 diabetes (p-value = 0.980) by smoking; myocardial infarction (p-value = 0.300), stroke (p-value = 0.607), hypertension (p-value <0.001) and type 2 diabetes (p-value = 0.081) by alcohol consumption; myocardial infarction (p-value = 0.590), stroke (p-value = 0.505) and hypertension (p-value = 0.029) by family history of cardiovascular disease; type 2 diabetes (p-value = 0.952) by family history of diabetes; and myocardial infarction (p-value = 0.334), stroke (p-value = 0.818), hypertension (p-value <0.001) and type 2 diabetes (p-value = 0.012) by sex.
Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals











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 frequency and various incident cancer outcomes. 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 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 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 terms – stomach cancer (p-value = 0.274), colon cancer (p-value = 0.440), rectum cancer (p-value = 0.107), lung cancer (p-value = 0.016), liver cancer (p-value = 0.129), pancreas cancer (p-value = 0.460), head & neck cancer (p-value = 0.488), kidney cancer (p-value = 0.285), gallbladder cancer (p-value = 0.970), and esophagus cancer (p-value = 0.263) by body mass index; stomach cancer (p-value = 0.699), colon cancer (p-value = 0.932), rectum cancer (p-value = 0.610), lung cancer (p-value = 0.492), liver cancer (p-value = 0.405), pancreas cancer (p-value = 0.338), head & neck cancer (p-value = 0.562), kidney cancer (p-value = 0.280), gallbladder cancer (p-value = 0.295), and esophagus cancer (p-value = 0.092) by smoking ; stomach cancer (p-value = 0.655), colon cancer (p-value = 0.977), rectum cancer (p-value = 0.433), lung cancer (p-value = 0.387), liver cancer (p-value = 0.704), pancreas cancer (p-value = 0.711), head & neck cancer (p-value = 1.000), kidney cancer (p-value = 0.336), gallbladder cancer (p-value = 0.350), and esophagus cancer (p-value = 0.550) by alcohol consumption ; stomach cancer (p-value = 0.996), colon cancer (p-value = 0.399), rectum cancer (p-value = 0.478), lung cancer (p-value = 0.007), liver cancer (p-value = 0.337), pancreas cancer (p-value = 0.086), head & neck cancer (p-value = 0.712), kidney cancer (p-value = 0.319), gallbladder cancer (p-value = 0.766), and esophagus cancer (p-value = 0.098) by family history of cancer; and stomach cancer (p-value = 0.405), colon cancer (p-value = 0.957), rectum cancer (p-value = 0.106), lung cancer (p-value = 0.063), liver cancer (p-value = 0.278), pancreas cancer (p-value = 0.265), head & neck cancer (p-value = 0.907), kidney cancer (p-value = 0.967), gallbladder cancer (p-value = 0.548), and esophagus cancer (p-value = 0.256) by sex. Abbreviations: HR – Hazard Ratio; CI – Confidence Intervals

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