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Physical Inactivity and Long-Term Rates of Community-Acquired Sepsis

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Abstract

OBJECTIVE—The authors sought to determine the association between physical inactivity (characterized by exercise and television watching levels) and long-term rates of community-acquired sepsis.

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AUTHORSHIP

HEW and MMS conceived the study. HEW and MMS organized and oversaw data collection. HEW, MMS and GH obtained funding for the study. HEW and RG conducted the analysis, and all authors contributed to review of results. HEW drafted the manuscript, and all authors contributed to its editorial review and revision. HEW assumes responsibility for the work as a whole.

CONFLICTS OF INTEREST

Dr. Safford reports the following potential conflicts of interest: Amgen - salary support to study patterns of statin use in Medicare and other large databases; diaDexus - salary support for a research grant on lipids and CHD outcomes; diaDexus - consulting to help with FDA application; NIH, AHRQ - salary support for research grants

Drs. Wang, Griffin, Baddley, Judd and Howard do not report any related conflicts of interest.

METHODS—Population-based cohort study of 30,183 adult (>45 years) community-dwelling participants. Subjects reported weekly exercise (low=none, medium=1-3 times/week, high=≥4 times/week) and daily television watching (low=<1 hour/day, medium=1-3 hours/day, high=≥4 hours/day) levels. The authors evaluated the association between exercise, television watching and rates of sepsis, defined as hospital treatment for a serious infection with ≥2 Systemic Inflammatory Response Syndrome (SIRS) criteria.

RESULTS—Among 30,183 participants, 1,500 experienced a sepsis event. Reported weekly exercise was: high 8,798 (29.2%), medium 10,695 (35.4%), and low 10,240 (33.9%). Where available, reported daily television watching was: low 4,615 (19.6%), medium 11,587 (49.3%) and high 7,317 (31.1%). Decreased weekly exercise was associated with increased adjusted sepsis rates (high – referent; medium HR 1.02, 95% CI 0.96-1.20; low 1.33, 1.13-1.56). Daily television watching was not associated with sepsis rates. Sepsis rates were highest among those with both low exercise and high television watching levels (HR 1.49, 95% CI: 1.10-2.01).

CONCLUSIONS—Physical inactivity may be associated with increased long-term rates of community-acquired sepsis.

Keywords

sepsis; infections; epidemiology; physical activity; diet; exercise; sedentary behavior

INTRODUCTION

Physical inactivity is prevalent in over half of United States adults, higher than other modifiable risk factors.(Macera, Jones et al. 2003) Physical activity involves a spectrum encompassing low through high metabolic activities.(Tremblay, Colley et al. 2010) An important element in this continuum is exercise, which has been associated with a host of health benefits, including reductions in coronary heart disease risk factors, cardiovascular disease, stroke and all-cause mortality.(Gibbons, Blair et al. 1983; Wood, Haskell et al. 1983; Kannel, Wilson et al. 1985; Blair, Kohl et al. 1989; Kiely, Wolf et al. 1994; Kokkinos 2012; Sluik, Buijsse et al. 2012) Another important element of physical activity is sedentary behavior, most commonly represented by television watching.(Hu, Leitzmann et al. 2001; Hu, Li et al. 2003; Grontved and Hu 2011) Television watching has been associated with increased risks of obesity, diabetes, cardiovascular disease, metabolic syndrome, cancer, psychosocial health, and all-cause mortality.(Hu, Leitzmann et al. 2001; Hu, Li et al. 2003; Dunstan, Salmon et al. 2007; Dunstan, Barr et al. 2010; Grontved and Hu 2011)

Sepsis, the syndrome of microbial infection complicated by systemic inflammation, is a major public health problem in the United States.(Dellinger, Levy et al. 2013) Each year, individuals with severe sepsis account for over 750,000 hospitalizations, 570,000 Emergency Department visits, and 200,000 deaths in the United States.(Angus, Linde-Zwirble et al. 2001; Wang, Shapiro et al. 2007) While international campaigns have highlighted the importance of early recognition and aggressive care in improving sepsis outcomes, relatively little attention has focused on the precursors of sepsis; that is, identification of the individuals at greatest risk for developing the condition.(Dellinger, Levy et al. 2013)

There are plausible connections between physical inactivity and one's risk of developing sepsis. For example, prior human and animal studies suggest associations between physical inactivity, immune function and susceptibility to upper respiratory infections.(Friman and Wesslen 2000; Walsh, Gleeson et al. 2011; Araujo, Campos et al. 2012; Gunzer, Konrad et al. 2012; Liebetanz, Gerber et al. 2012)(Matthews, Ockene et al. 2002; Chubak, McTiernan et al. 2006; Barrett, Hayney et al. 2012) We have previously observed associations between chronic medical conditions and increased rates of sepsis, including many associated with lack of physical activity.(Wang, Shapiro et al. 2012) Television watching has been associated with poor dietary habits, and obesity - a major consequence of poor diet and physical inactivity - is also independently associated with increased rates of sepsis.(Hu, Leitzmann et al. 2001; Hu, Li et al. 2003; Wang, Griffin et al. 2013)

In this we study we sought to determine the association between physical inactivity (characterized by exercise and television watching) and long-term rates of community-acquired sepsis.

METHODS

Study Design

This study utilized data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a national, population-based, longitudinal cohort. The study received approved by the Institutional Review Board of the University of Alabama at Birmingham.

Selection of Participants

REGARDS is one of the largest ongoing national cohorts of community-dwelling individuals in the US, encompassing 30,239 individuals 45 years old.(Howard, Cushman et al. 2005) Designed to evaluate reasons for geographic and racial variations in stroke mortality, REGARDS includes individuals from all regions of the continental US. The study oversampled participants in the Southeastern US, with 21% of the cohort originating from the coastal plains of North Carolina, South Carolina and Georgia (the "buckle" of the stroke belt), and 35% originating from the remainder of North Carolina, South Carolina and Georgia plus Tennessee, Mississippi, Alabama, Louisiana and Arkansas (the "stroke belt"). The cohort is 42% African American and 45% male, and 69% of individuals are >60 years old. REGARDS does not include Hispanics, where stroke mortality disparities are small-to-non-existent.

REGARDS enrolled participants during 2003-7. The study obtained baseline data for each participant through phone interviews and in-person evaluations. Baseline data included medical history, functional status, health behaviors, physical characteristics (height, weight), physiologic measures (blood pressure, pulse, electrocardiogram), and an inventory of medications. Each participant provided blood and urine specimens. Participants completed self-administered questionnaires regarding diet, family history of diseases, psychosocial factors and prior residences. On a semi-annual basis, REGARDS contacted each participant to determine the date, location and attributed reason for all emergency department visits and hospitalizations during the follow-up interval. If the participant died, the study team

reviewed death certificates and related medical records and interviewed proxies to ascertain the circumstances of the participant's death.

Identification of Sepsis Events

We reviewed all reported hospitalizations and Emergency Department visits attributed by participants to a serious infection. We identified serious infections using taxonomies developed by Angus, et al. (Angus, Linde-Zwirble et al. 2001). Two trained abstractors independently reviewed all pertinent medical records to confirm the presence of a serious infection on initial hospital presentation. The abstractors also confirmed if the serious infection was a major reason for hospitalization. Medical record review included clinical and laboratory information from the first 28-hours of hospitalization, a time period encompassing Emergency Department and up to one full day of inpatient treatment. The abstractors adjudicated discordances, with additional physician-level review as needed.

Using international consensus definitions, we defined community-acquired sepsis as hospital treatment for an infection with two or more systemic inflammatory response syndrome (SIRS) criteria, including 1) heart rate >90 beats/minute, 2) fever (temperature >38.3°C or <36°C), 3) tachypnea (>20 breaths/min) or PCO₂<32 mmHg, and 4) leukocytosis (white blood cells [WBC] >12,000 or <4,000 cells/mm³ or >10% band forms). Presentation to the hospital consisted of the time of Emergency Department triage or admission to inpatient unit (for participants admitted directly to the hospital). To allow for acute changes in the participant's condition during early hospitalization, we used vital signs and laboratory test results for the initial 28-hours of hospitalization. Our study focused on individuals presenting to the hospital or Emergency Department with community-acquired sepsis. We did not include "hospital-acquired" sepsis developing at later points of hospitalization. We did not include organ dysfunction in the definition of sepsis. Initial review of 1,349 hospital records indicated excellent inter-rater agreement for presence of a serious infection (kappa=0.92) and the presence of sepsis (kappa=0.90) upon hospital presentation.

We included all sepsis events identified during the 10-year timeframe 2003-2012.

Definition of Exercise and Television Watching

We defined physical inactivity in terms of exercise and television watching. During their initial phone interview for the REGARDS study, participants reported their weekly frequency of exercise based upon the question, "How many times per week do you engage in intense physical activity, enough to work up a sweat?" The study categorized weekly exercise as none, 1-3 times per week, and 4 or more times per week. Participants reported weekly television or video watching frequency on a written survey administered during the initial in-person examination. Television and video watching categories included none, 1-6 hours/week, 1 hour/day, 2 hours/day, 3 hours/day, and 4+ hours/day.

Covariates

Sociodemographic characteristics included age, sex, race, geographic region, self-reported annual household income and self-reported education (years of school). To account for the sampling strategy used to recruit the REGARDS cohort, we defined geographic region as

participant residence in the stroke “buckle,” stroke “belt” and elsewhere, as described previously.(Howard 1999; Howard, Cushman et al. 2005)

Health behaviors included tobacco and alcohol use, and exercise. We defined smoking status as current, past and never. We defined alcohol use according to the National Institute on Alcohol Abuse and Alcoholism classification; i.e., moderate (1 drink per day for women or 2 drinks per day for men) and heavy alcohol use (>1 drink per day for women and >2 drinks per day for men).(2005)

Television watching has been associated with poor dietary habits.(Hu, Leitzmann et al. 2001; Hu, Li et al. 2003) We characterized diet in terms of adherence to a Mediterranean Diet pattern, which has been associated with improved health outcomes, including reductions in cardiovascular disease and death.(Estruch, Ros et al. 2013) REGARDS participants completed a comprehensive food questionnaire documenting the frequency of consumption of items in nine food groups or components, including cereals, vegetables, fruits and nuts, legumes, fish, monounsaturated to saturated fat ratio, and moderate alcohol consumption, meat and dairy food products. We assigned a value of 1 for intake greater or equal than the median for food groups contributing to greater adherence to a Mediterranean diet; specifically, cereals, vegetables, fruits and nuts, legumes, fish, monounsaturated to saturated fat ratio, and moderate alcohol consumption. We also assigned a value of 1 for meat and dairy food product consumption less than the median. We summed the food group scores to yield an overall score ranging from 0 to 9, with higher scores indicating greater adherence to the Mediterranean Diet.

Obesity included individuals with elevated body mass index (BMI) or waist circumference (WC). Following standardized protocols, REGARDS examiners measured weight, height and WC of each participant at the beginning of the study. We defined elevated BMI as values $>30 \text{ kg/m}^2$, which is the cutoff for obesity in the United States.(2012) Examiner measured WC at a point midway between the lowest rib and the iliac crest with the subject standing. We defined elevated WC as values $>102 \text{ cm}$ for males and $>88 \text{ cm}$ for females. (Janssen, Katzmarzyk et al. 2002)

Chronic medical conditions included diabetes, hypertension, history of myocardial infarction, history of stroke, chronic kidney disease, and chronic lung disease. Diabetes included a fasting glucose $\geq 126 \text{ mg/L}$ (or a glucose $\geq 200 \text{ mg/L}$ for those not fasting) or the use of insulin or oral hypoglycemic agents. Hypertension consisted of systolic blood pressure $\geq 140 \text{ mm Hg}$, diastolic blood pressure $\geq 90 \text{ mm Hg}$, or the self-reported use of antihypertensive agents. Participants self-reported history of myocardial infarction or stroke. Chronic kidney disease included individuals with an estimated glomerular filtration rate $<60 \text{ ml/min/1.73 m}^2$, calculated using the CKD-EPI equation.(Levey, Stevens et al. 2009) Because REGARDS did not collect information on pulmonary conditions such as asthma and chronic obstructive pulmonary disease, we defined participant use of pulmonary medications as a surrogate for chronic lung disease. Obtained from each participant's medication inventory, pulmonary medications included beta agonists, leukotriene inhibitors, inhaled corticosteroids, combination inhalers, and other pulmonary medications such as ipratropium, cromolyn, aminophylline and theophylline.

Data Analysis

We conceptualized exercise and television watching as the primary exposures of interest in the analysis. Using a chi-square test, we first examined demographic, health behavioral and clinical characteristics differences between categories of exercise and television watching.

To estimate the associations between exercise, television watching and sepsis, we fit a series of multivariable Cox proportional hazards models. We limited the analysis to the first sepsis episode. Person-time at risk consisted of the time (days) from first in-person examination to the first episode of sepsis or the last follow-up interview, whichever came first. We defined exercise levels as low (none), medium (1-3 times/week) and high (4 times/week). We defined television watching levels as low (<1 hour/day), medium (1-3 hours/day) and high (4 hours/day). Multivariable adjustment accounted for demographic characteristics (age, sex, race, income, education, geographic region), health behaviors (smoking and alcohol use, exercise), obesity, adherence to a Mediterranean diet, and chronic medical conditions (diabetes, hypertension, myocardial infarction, stroke, chronic kidney disease, chronic lung disease).

We evaluated the [exercise X television watching] interaction in the multivariable model. We also examined interactions between exercise, television watching, and age, sex, race and geographic region. We fit a model separately assessing the associations of sepsis for different joint combinations of exercise and television watching. We tested the proportional hazards assumption of the Cox model using log-log plots and Schoenfeld residuals. We evaluated for potential collinearity between exercise and television watching by evaluating variance inflation factors. We conducted all analyses using Stata 12.2 (Stata, Inc, College Station, Texas).

RESULTS

From February 5, 2003 through December 31, 2012, among 30,183 participants, 2,553 experienced a serious infection, including 1,500 who experienced a hospitalization for community-acquired sepsis. The most common infection types associated with first sepsis events were pneumonia, kidney and urinary tract infections, and abdominal infections. (Table 1)

Weekly exercise data were available for 29,733 of 30,183 (98.5%) participants. Reported weekly exercise among REGARDS participants included: high exercise (4 times/week) 8,798 (29.2%), medium (1-3 times/week) 10,695 (35.4%), and low (none) 10,240 (33.9%). (Table 2) Exercise frequency was lower for older, female and black individuals, as well as those with lower annual income and education. Although exercise frequency was lower for current smokers, exercise frequency was higher among moderate and heavy alcohol users. Diet was similar between exercise levels. Exercise frequency was lower among those with obesity and chronic medical conditions.

Television watching data were available for 23,519 of 30,183 (77.9%) participants. Reported television watching among REGARDS participants included: low (<1 hour/day) 4,615 (19.6%), medium (1-3 hours/day) 11,587 (49.3%) and high (4 hours/day) 7,317 (31.1%).

(Table 3) Television watching levels were higher for older, female and black individuals, as well as those with lower annual income and education. Television watching was higher among current smokers. Most moderate and heavy alcohol users reported medium television watching levels. Television watching levels were higher among those with obesity and chronic medical conditions.

Median follow-up time was 6.6 years (IQR 5.1-8.1). Sepsis incidence was highest among those who reported no weekly exercise or 4 hours of daily television watching. (Table 4) On multivariable analysis, low exercise was independently associated with increased rates of sepsis, even after adjustment for demographics, tobacco and alcohol use, obesity, diet and chronic medical conditions. (Table 5) Television watching was not associated with rates of sepsis after adjustment for confounders.

The [exercise X television watching] interaction was not statistically significant. Interaction between exercise and age, sex, race and geographic region were not statistically significant. Interaction between television watching and age, sex, race and geographic region were also not statistically significant. When examining the joint association between exercise and television watching, individuals reporting both low exercise and high television watching exhibited the highest adjusted rates of sepsis. (Table 6)

Examination of log-log plots, Kaplan-Meier predicted survival plots, and Schoenfeld residuals verified that exercise and television watching satisfied the proportional hazards assumption. On collinearity analysis, the tolerance and variance inflation factor were 0.99 and 1.01, respectively, suggesting no collinearity between exercise and television watching.

DISCUSSION

In this study we observed associations between low weekly exercise and long-term rates of community-acquired sepsis. This relationship persisted even after adjustment for a range of potential confounders, indicating that the associations were not merely mediated by factors such as obesity and diet. While we did not observe an independent association between television watching and sepsis events, individuals reporting *both* low weekly exercise *and* high levels of daily television watching exhibited the highest rates of sepsis. These findings underscore the potential links between physical inactivity and long-term rates of sepsis.

In interpreting these results, one must consider that levels of television watching and exercise were based upon self-reports and may not encompass the full spectrum of sedentary behaviors.(Katzmarzyk, Church et al. 2009; Tremblay, Colley et al. 2010; Clark, Healy et al. 2011) Our analysis also assumed connections between baseline exercise and television watching and sepsis events over a 10-year span. However, REGARDS provided the best available data and presented one of the few opportunities to evaluate the connections between physical inactivity and long-term sepsis rates.

There are plausible connections between exercise and sepsis rates. Exercise has been associated with a host of immunologic alterations such as the reduction of Toll-like receptors expression on monocytes and macrophages, and inhibition of monocyte and macrophage infiltration of adipose.(Flynn and McFarlin 2006; Gleeson, McFarlin et al.

2006; Gleeson, Bishop et al. 2011) Sepsis is characterized by hyper-inflammatory response to microbial infection, and exercise is believed to have anti-inflammatory effects, including the increased production of anti-inflammatory cytokines.(3).(Gleeson, Bishop et al. 2011) Exercise and physical activity are associated with reduced levels of inflammatory markers, including high sensitivity C-reactive protein (hsCRP); we previously found that elevated hsCRP is associated with increased sepsis risk.(Geffken, Cushman et al. 2001; Abramson and Vaccarino 2002; Ford 2002; Yu, Ye et al. 2009)(Wang, Shapiro et al. 2012) Endothelial cell activation has been implicated in sepsis pathophysiology, and exercise is believed to mitigate endothelial dysfunction and inflammation.(Aird 2003; Ribeiro, Alves et al. 2010; Wang, Shapiro et al. 2013) Increased exercise and physical activity have been associated with reductions in cardiovascular disease, stroke, cancer, diabetes and dementia; these chronic medical conditions are known risk factors for sepsis.(Blair, Goodyear et al. 1984; Blair, Kohl et al. 1989; Warburton, Nicol et al. 2006; Kokkinos 2012) (Wang, Shapiro et al. 2012) Human trials have linked exercise with reduced acute respiratory infections. (Matthews, Ockene et al. 2002; Chubak, McTiernan et al. 2006; Barrett, Hayney et al. 2012)

Our observations suggested heightened sepsis rates among those with both low weekly exercise and high daily levels of television watching. As the most common form of sedentary behavior, television watching has been associated with increased risk of diabetes, cardiovascular disease, chronic kidney disease and obesity, factors that we have previously associated with increased sepsis risk.(Hu, Leitzmann et al. 2001; Mayer-Davis and Costacou 2001; Hu, Li et al. 2003; Dunstan, Salmon et al. 2005; Dunstan, Salmon et al. 2007; Lynch, White et al. 2010; Grontved and Hu 2011; Inoue, Sugiyama et al. 2012) In contrast to the anti-inflammatory effect of exercise, sedentary behavior has been associated with increases in serum markers of inflammation, including hsCRP.(Healy, Matthews et al. 2011) As discussed previously, we have identified an association with elevated hsCRP and risk of sepsis.(Wang, Shapiro et al. 2012)

While our study does not verify a causal relationship between physical inactivity and sepsis, the observations highlight the potential role of preventive health as a strategy for reducing long-term rates of sepsis. Current sepsis clinical and scientific initiatives focus upon the acute care and course of the condition. Relatively little attention has focused upon the identification of individuals at greatest risk for developing sepsis nor upon strategies for sepsis prevention. Some of the most important public health gains have originated from efforts to prevent deadly health conditions such as cardiovascular disease and stroke. A similar approach could result in major reductions in sepsis morbidity and mortality. Along these lines, exercise and television watching may present important and novel opportunities for reducing rates of sepsis because of their modifiable nature and widespread prevalence in the United States. Less than half of the United States adults participate in regular moderate-to-vigorous physical activity.(Sapkota, Bowles et al. 2005) US adults watch an average of 29-34 hours of television per week.(Grontved and Hu 2011) Given the pervasive nature of physical inactivity, organized efforts targeting these risk factors could result in significant advancements in sepsis care and prevention.

LIMITATIONS

Television watching and exercise may not encompass the full spectrum of sedentary behaviors.(Katzmarzyk, Church et al. 2009; Tremblay, Colley et al. 2010; Clark, Healy et al. 2011) Participants may not have accurately reported their weekly exercise or television watching levels. We also did not have information on the duration or intensity of exercise or the patterns of television watching. We could not account for changes in exercise of television watching levels over time. Additional study using more precise measures of physical activity would be appropriate. Our study reflects participants from the US population; the optimal methods for defining and assessing physical inactivity may vary internationally.

REGARDS did not measure global physical activity, which may have stronger connections with sepsis rates than self-reported exercise or television watching levels.(Wareham, Jakes et al. 2003; Bull, Maslin et al. 2009) Measurement of activity among REGARDS participants using accelerometers is the objective of a separate study.

While we adjusted for a range of potential confounders, the associations between exercise levels, television watching and sepsis rates may have been influenced by other variables such as vaccination or access to healthcare. Low-level exercise may also indicate individuals less willing to use and access preventive services or timely acute care.

REGARDS is not a surveillance study, and thus we may not have identified all sepsis events. However, misclassification of sepsis events should be similar between exercise and television watching categories, and thus the analysis should present underestimates of the true association. By design, the REGARDS cohort includes only African Americans and whites, and thus these results may not generalize to other ethnic groups.

CONCLUSION

In this analysis of the REGARDS cohort, individuals reporting low weekly levels of exercise (especially those with high daily levels of television watching) exhibited increased adjusted long-term rates of community-acquired sepsis. Physical inactivity may provide a target for sepsis prevention.

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HIGHLIGHTS

- Sepsis is a major public health problem.
- No studies have linked physical inactivity with long-term sepsis rates.
- We studied 30,183 subjects in the national REGARDS cohort.
- Low weekly exercise (<1 hr/day) was associated with increased sepsis rates.

TABLE 1

Infection types associated with first hospitalizations for sepsis. Total of 1,500 first sepsis events.

Infection Type	Number of First Sepsis Hospitalizations N (%)
Pneumonia	592 (39.5)
Kidney and Urinary Tract Infections	251 (16.7)
Abdominal	230 (15.3)
Bronchitis, Influenza and other Lung Infections	137 (9.1)
Skin and Soft Tissue	121 (8.1)
Sepsis	98 (6.5)
Fever of Unknown Origin	29 (1.9)
Catheter (IV / Central / Dialysis)	6 (0.4)
Surgical Wound	10 (0.7)
Meningitis	5 (0.3)
Unknown/Other	21 (1.4)

TABLE 2

Baseline characteristics of REGARDS participants, stratified by quantity of weekly exercise. Weekly exercise levels available for 29,733 of 30,183 (98.5%) participants.

Variable	High Exercise (4 times/week) (n=8,798) (col %)	Medium Exercise (1-3 times/week) (n=10,695) (col %)	Low Exercise (none) (n=10,240)(col %)	P-value
Demographics				
Age				
<50 years	5.1	6.0	4.1	<0.001
50-59	24.7	29.4	24.5	
60-69	39.4	37.6	36.1	
70-79	24.7	21.6	25.7	
80	6.2	5.4	9.5	
Sex				
Male	54.0	45.3	36.6	<0.001
Female	46.0	54.7	63.4	
Race				
White	63.2	58.5	54.6	<0.001
Black	36.8	41.5	45.4	
Geographic Region				
Non-Belt	43.7	44.6	45.1	0.35
“Stroke Belt”	34.8	34.5	34.6	
“Stroke Buckle”	21.5	20.8	20.3	
Income				
<\$20,000	15.9	15.0	23.3	<0.001
\$20,000-34,000	23.4	23.3	25.8	
\$35,000-74,000	30.9	32.0	26.1	
\$75,000	17.6	18.6	11.5	
Unknown	12.3	11.1	13.3	
Education				
Less than High School	11.6	9.9	15.8	<0.001
High School Graduate	25.6	23.6	28.4	
some College	26.1	27.1	27.3	
College Graduate	36.7	39.4	28.5	
Missing	0.0	0.1	0.1	
Health Behaviors				
Tobacco Use				
Never	43.7	47.8	43.5	<0.001
Past	42.7	38.5	39.1	
Current	13.2	13.3	17.1	
Missing	0.4	0.4	0.3	
Alcohol Use				

Variable	High Exercise (4 times/week) (n=8,798) (col %)	Medium Exercise (1-3 times/week) (n=10,695) (col %)	Low Exercise (none) (n=10,240)(col %)	P-value
None	57.5	59.2	67.0	<0.001
Moderate	35.8	35.4	27.4	
Heavy	4.9	3.5	3.4	
Missing	1.8	1.9	2.1	
Obesity (abnormal BMI or WC)	44.2	53.2	61.8	<0.001
Missing	0.2	0.1	0.2	
Mediterranean Diet Score (median, IQR)	5 (3-6)	4 (3-6)	4 (3-5)	<0.001*
Missing (%)	27.4	27.8	33.0	
Chronic Medical Conditions				
Chronic Kidney Disease	8.4	9.1	14.8	<0.001
Chronic Lung Disease	7.8	8.5	11.1	<0.001
Diabetes	19.3	20.9	27.2	<0.001
Hypertension	54.4	57.2	65.3	<0.001
Myocardial Infarction	12.0	10.9	14.5	<0.001
Stroke	5.3	4.9	8.9	<0.001

* From Kruskal-Wallis test.

TABLE 3

Baseline characteristics of REGARDS participants, stratified by quantity of daily television watching. Television watching levels available for 23,519 of 30,183 (77.9%) participants.

	Low Television Watching (1 hour/day) (n=4,615) (col %)	Medium Television Watching (1-3 hours/day) (n=11,587) (col %)	High Television Watching (4 hours/day (n=7,317) (col %)	P-value
Demographics				
Age				
<50 years	6.2	4.1	4.2	<0.001
50-59	29.1	24.6	23.6	
60-69	36.6	37.8	39.9	
70-79	21.7	25.8	25.3	
80	6.4	7.7	7.0	
Sex				
Male	44.5	48.2	39.5	<0.001
Female	55.5	51.8	60.5	
Race				
White	69.0	70.9	49.0	<0.001
Black	31.0	29.1	51.0	
Geographic Region				
Non-Belt	44.6	43.2	43.6	0.001
“Stroke Belt”	33.8	34.0	36.0	
“Stroke Buckle”	21.5	22.8	20.4	
Income				
<\$20,000	14.0	12.6	26.9	<0.001
\$20,000-34,000	19.3	24.0	28.0	
\$35,000-74,000	30.7	33.4	25.2	
\$75,000	24.1	18.2	7.4	
Unknown	11.9	11.8	12.5	
Education				
Less than High School	9.0	8.1	17.3	<0.001
High School Graduate	21.5	24.0	32.3	
Some College	23.2	28.4	27.1	
College Graduate	46.2	39.5	23.3	
Missing	0.0	0.0	0.1	
Health Behaviors				
Tobacco Use				
Never	52.4	45.6	38.4	<0.001
Past	37.4	42.2	41.6	
Current	9.8	11.8	19.7	
Missing	0.5	0.4	0.3	

	Low Television Watching (1 hour/day) (n=4,615) (col %)	Medium Television Watching (1-3 hours/day) (n=11,587) (col %)	High Television Watching (4 hours/day) (n=7,317) (col %)	P-value
Alcohol Use				
None	58.9	57.6	64.9	<0.001
Moderate	35.8	36.4	28.8	
Heavy	3.9	4.4	4.1	
Missing	1.3	1.7	2.2	
Obesity (abnormal BMI or WC)	43.3	49.6	61.2	<0.001
Missing	0.1	0.1	0.2	
Mediterranean Diet Score (median, IQR)	5 (3-6)	4 (3-6)	4 (3-5)	<0.001
Missing	12.1	10.2	13.2	
Chronic Medical Conditions				
Chronic Kidney Disease	8.1	10.1	13.1	<0.001
Chronic Lung Disease	8.5	8.6	11.3	
Diabetes	17.0	19.0	27.2	<0.001
Hypertension	49.7	56.5	65.8	
Myocardial Infarction	10.7	11.8	14.0	<0.001
Stroke	4.4	4.8	8.2	

*
From Kruskal-Wallis test.

TABLE 4

Sepsis incidence rates by exercise and television watching category.

Activity	Person-Time (person-years)	First Sepsis Events	Incidence (Sepsis events per 1,000 person years)
Exercise			
High (4 times/week)	55,471	379	6.8 (6.2-7.6)
Medium (1-3 times/week)	68,283	452	6.6 (6.0-7.3)
Low (none)	60,099	642	10.7 (9.9-11.5)
Television Watching			
Low (1 hour/day)	29,969	204	6.8 (5.9-7.8)
Medium (2-3 hours/day)	74,742	543	6.6 (6.0-7.3)
High (4 hours/day)	44,578	469	10.7 (9.9-11.5)
Overall	186,420	1,498	8.0 (7.6-8.4)

TABLE 5

Multivariable hazard ratios for associations between exercise, television watching and first-sepsis events. Total of 1,500 first-sepsis events. Television watching and exercise were both included in the models.

Activity	Unadjusted Model	Add demographics, [*] tobacco and alcohol use	Add obesity	Add diet	Add chronic medical conditions ^{**}
Quantity of Exercise					
High (4 times/week)	Referent	Referent	Referent	Referent	Referent
Medium (1-3 times/week)	0.93 (0.80-1.09)	1.04 (0.89-1.21)	1.01 (0.86-1.18)	1.02 (0.86-1.20)	1.02 (0.86-1.20)
Low (none)	1.53 (1.33-1.71)	1.53 (1.31-1.76)	1.43 (1.24-1.66)	1.43 (1.22-1.67)	1.33 (1.13-1.56)
Quantity of Television Watching					
Low (1 hour/day)	Referent	Referent	Referent	Referent	Referent
Medium (2-3 hours/day)	1.04 (0.88-1.22)	0.91 (0.77-1.08)	0.89 (0.76-1.05)	0.92 (0.77-1.10)	0.94 (0.79-1.13)
High (4 hours/day)	1.43 (1.21-1.69)	1.22 (1.03-1.45)	1.17 (0.99-1.40)	1.24 (1.03-1.49)	1.16 (0.95-1.40)

* Age decile, sex, race, geographic region, income, education.

** Chronic kidney disease, chronic lung disease, diabetes, hypertension, myocardial infarction, stroke.

TABLE 6

Multivariable hazard ratios for joint associations between exercise and television watching levels and first-sepsis events. Total of 1,500 first-sepsis events.

Exercise and Television Watching Level		Unadjusted HR (95% CI) for Sepsis	Adjusted* HR (95% CI) for Sepsis
High exercise (4 times/week)	+ Low television watching (1 hour/day)	Referent	Referent
High exercise	+ Medium television watching (2-3 hours/day)	1.00 (0.75-1.33)	0.84 (0.61-1.15)
High exercise	+ High television watching (4 hours/day)	1.31 (0.96-1.79)	1.06 (0.75-1.50)
Medium exercise (1-3 times/week)	+ Low television watching (1 hour/day)	0.89 (0.64-1.25)	0.92 (0.63-1.33)
Medium exercise	+ Medium television watching (2-3 hours/day)	0.98 (0.74-1.29)	0.95 (0.70-1.28)
Medium exercise	+ High television watching (4 hours/day)	1.17 (0.87-1.58)	0.98 (0.70-1.37)
Low exercise (none)	+ Low television watching (1 hour/day)	1.41 (1.01-1.98)	1.15 (0.78-1.09)
Low exercise	+ Medium television watching (2-3 hours/day)	1.43 (1.09-1.89)	1.11 (0.81-1.51)
Low exercise	+ High television watching (4 hours/day)	2.22 (1.70-2.90)	1.49 (1.10-2.01)

* Adjusted for age decile, sex, race, geographic region, income, education, obesity, Mediterranean diet score, and history of chronic kidney disease, chronic lung disease, diabetes, hypertension, myocardial infarction or stroke.