



## 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.

**Methods:** The study utilized a population-based cohort of 30,183 adult ( $\geq 45$  years) community dwelling adults. Subjects reported weekly exercise (low = none, medium = 1–3 times/week, high =  $\geq 4$  times/week) and daily television watching (low =  $< 1$  h/day, medium = 1–3 h/day, high =  $\geq 4$  h/day) levels. The authors evaluated the association between exercise, television watching and rates of sepsis, defined as hospital treatment for a serious infection with  $\geq 2$  Systemic Inflammatory Response Syndrome (SIRS) criteria.

**Results:** Among 30,183 participants, 1500 experienced a sepsis event. Reported weekly exercise was: high 8798 (29.2%), medium 10,695 (35.4%), and low 10,240 (33.9%). Where available, reported daily television watching was: low 4615 (19.6%), medium 11,587 (49.3%) and high 7317 (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.

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### Introduction

Physical inactivity is prevalent in over half of United States adults, higher than other modifiable risk factors (Macerata et al., 2003). Physical activity involves a spectrum encompassing low through high metabolic activities (Tremblay 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 (Blair et al., 1989; Gibbons et al., 1983; Kannel et al., 1985; Kiely et al., 1994; Kokkinos, 2012; Sluik et al., 2012; Wood et al., 1983). Another important element of physical activity is sedentary behavior, most commonly represented by television watching (Grontved and Hu, 2011; Hu et al., 2001, 2003). Television watching has been associated with increased risks of obesity, diabetes, cardiovascular disease, metabolic syndrome, cancer, psychosocial health, and all-cause mortality (Dunstan et al., 2007, 2010; Grontved and Hu, 2011; Hu et al., 2001, 2003).

Sepsis, the syndrome of microbial infection complicated by systemic inflammation, is a major public health problem in the United States (Dellinger 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 et al., 2001; Wang 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 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 (Araujo et al., 2012; Barrett et al., 2012; Chubak et al., 2006; Friman and Wesslen, 2000; Gunzer et al., 2012; Liebetanz et al., 2012; Matthews et al., 2002; Walsh et al., 2011). We have previously observed associations between chronic medical conditions and increased rates of sepsis, including many associated with lack of physical activity (Wang et al., 2012). Television watching has been associated with poor dietary habits, and obesity – a major consequence of poor diet and physical

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inactivity – is also independently associated with increased rates of sepsis (Hu et al., 2001, 2003; Wang et al., 2013c).

In this 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 approval 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  $\geq 45$  years old (Howard 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. (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 h 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/min, 2) fever (temperature  $> 38.3$  °C or  $< 36$  °C), 3) tachypnea ( $> 20$  breaths/min) or  $PCO_2 < 32$  mm Hg, and 4) leukocytosis (white blood cells [WBC]  $> 12,000$  or  $< 4000$  cells/mm<sup>3</sup> 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 h 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 1349 hospital records indicated excellent inter-rater agreement for the 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 h/week, 1 h/day, 2 h/day, 3 h/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 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) (Anon, 2005).

Television watching has been associated with poor dietary habits (Hu et al., 2001, 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 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  $> 30$  kg/m<sup>2</sup>, which is the cutoff for obesity in the United States (Anon, 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  $> 102$  cm for males and  $> 88$  cm for females (Janssen 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  $\geq 126$  mg/L (or a glucose  $\geq 200$  mg/L for those not fasting) or the use of insulin or oral hypoglycemic agents. Hypertension consisted of systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  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  $< 60$  ml/min/1.73 m<sup>2</sup>, calculated using the CKD-EPI equation (Levey 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.

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