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Occupational epidemiology in vulnerable populations: Occupational physical activity and cerebrovascular disease in older women and parental occupational exposures and childhood cancer

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by

Clinton James Hall

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ABSTRACT OF DISSERTATION

Occupational epidemiology in vulnerable populations:
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and parental occupational exposures and childhood cancer

by

Clinton James Hall

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Professor Beate R. Ritz, Chair

Occupation has a profound impact on worker health. Some working populations, such as older workers and pregnant women, are inherently vulnerable to hazardous exposures; identifying and quantifying occupational risk factors in these populations is important to the health and wellbeing of the population as a whole. This dissertation is composed of three independent exercises in occupational epidemiology that examine associations between (1) occupational physical activity and cerebrovascular disease in a cohort of older women; (2) parental occupational exposure to livestock or animal dust and the risk for childhood cancer in offspring; and (3) parental occupation and the risk for childhood germ cell tumors in Denmark.

The first analysis in this dissertation is a prospective cohort study of 31,270 women aged 30-74 years and employed outside the home at study enrollment. Information on occupational physical activity (OPA) for current job, longest held job, and cumulatively for all jobs held since age 18, in addition to information on lifestyle factors, was assessed via interviews at study enrollment. After classifying OPA into four categories ranked by intensity (mostly sitting, sitting and standing equally, mostly standing, and mostly dynamic work), we used Cox proportional hazard regression models adjusted for socio-demographic, biologic, and behavioral factors to estimate the risk of incident stroke and transient ischemic attack (TIA) across levels of OPA. There were 715 incident diagnoses of stroke (n=441) and TIA (n=274) reported by participants or next of kin over an average follow up of 6 years. Compared to mostly sitting, mostly dynamic OPA at the current job was associated with an increased risk for TIA (hazards ratio [HR]=1.65; 95% confidence interval [CI]=1.07-2.48), while mostly dynamic OPA at the longest held job was associated with an increased risk of stroke (HR=1.45; 95% CI=1.06-1.97). Associations were stronger among women without cardiovascular disease or hypertension at baseline.

The second analysis in this dissertation is a population-based case-control study of 4,474 childhood cancer cases diagnosed 1968-2015 in Denmark and 422,022 birth year- and sex-matched controls. Using a job-exposure matrix, we identified parental occupational exposure to livestock or animal dust. Using multivariable conditional logistic regression, we estimated an increased risk for all central nervous system tumors in the offspring of fathers occupationally exposed to livestock or animal dust from the index child's birth to cancer diagnosis (odds ratio [OR]=1.27; 95% CI=1.00-1.63). There was an increased risk for astrocytoma in the offspring of mothers exposed from conception to birth (OR=1.89; 95% CI=1.00-3.57) and an increased risk for neuroblastoma in the offspring of mothers exposed from birth to diagnosis (OR=1.88; 95%

CI=0.99-3.56). We examined births 1989+ to assess a period when exposures were more intensive due to a policy change regulating farm size and estimated a decreased risk for acute lymphoblastic leukemia in the offspring of fathers exposed after birth (OR=0.56; 95% CI=0.32-1.00).

The final analysis in this dissertation is a population-based case-control study of parental occupation and the risk for childhood germ cell tumors (GCTs) in offspring. Utilizing a linked database of five nationwide Danish registries, this study consisted of 164 childhood GCT cases (<17 years old) diagnosed 1968-2015 and 15,513 birth year- and sex-matched controls. Conditional multivariable logistic regression was used to analyze the association between paternal and maternal occupation and childhood GCT risk in offspring, stratifying by common histologic subtypes (i.e., yolk sac tumor and teratoma) when possible. Parental occupational exposure to specific chemicals and social contact was assessed via JEMs applied to the individual parental employment histories. We found an increased risk of GCTs in the offspring of mothers occupationally exposed to high/very high social contact from child's conception to birth, especially among yolk sac tumors (OR=3.50; 95% CI=1.65, 7.43); this association persisted when examining maternal occupational exposure from birth to diagnosis (OR=2.77; 95% CI=1.29, 5.57). We also observed an elevated risk of all GCTs in the offspring of mothers who worked in the textile, clothing, and leather industry from birth to diagnosis (OR=2.19; 95% CI=1.09, 4.40). Paternal employment in the agriculture, forestry, and fishing industry from child's birth to diagnosis was associated with an increased risk of teratomas in offspring (OR=2.73; 95% CI=1.14, 6.78).

The dissertation of Clinton James Hall is approved.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Acute lymphoblastic leukemia (ALL)

Body mass index (BMI)

Cardiovascular disease (CVD)

Central nervous system (CNS)

Confidence interval (CI)

Developmental origins of health and disease (DOHaD)

Germ cell tumor (GCT)

Hazards ratio (HR)

Job-exposure matrix (JEM)

Leisure time physical activity (LTPA)

International Agency for Research on Cancer (IARC)

International Classification of Childhood Cancer (ICCC)

International Classification of Diseases for Oncology (ICD-O)

International Standard Industrial Classification for All Economic Activities (ISIC)

Metabolic equivalent task (MET)

Methicillin-resistant Staphyloccussaureas (MRSA)

National Institute for Occupational Safety and Health (NIOSH)

National Occupational Research Agenda (NORA)

Odds ratio (OR)

Occupational physical activity (OPA)

Occupational Safety and Health Administration (OSHA)

Population attributable risk (PAR)

Socioeconomic status (SES)

Transient ischemic attack (TIA)

World Health Organization (WHO)

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Hall C, Ritz B, Cockburn M, Davidson TB, Heck JE. Risk of malignant childhood germ cell tumors in relation to demographic, gestational and perinatal characteristics. *Cancer Epidemiol.* 2017. DOI 10.1016/j.canep.2016.12.002.

Laster M, Soohoo M, Hall C, Streja E, Rhee CM, Ravel VA, Reddy U, Norris KC, Salusky IB, Kalantar-Zadeh K. Racial-ethnic disparities in mortality and kidney transplant outcomes among pediatric dialysis patients. *Pediatr. Nephrol.* 2016. DOI 10.1007/s00467-016-3530-2.

Chapter 1. Introduction and background

1.1 Occupational epidemiology

Physicians and other health professionals have noted the impact of occupation on health for centuries; Bernardino Ramazzini, widely considered the "father of occupational medicine," described a variety of occupation-related diseases and their causes in his book *De Morbis Artificum*, published in 1700.[1] Even some of the earliest epidemiologic investigations began by examining occupation and occupation-related exposures: In 1775—decades before Jon Snow removed the handle from the water pump on Broad Street—a man named Percival Pott identified soot as the cause of scrotal cancer in London chimney sweeps. This is largely considered to be the first instance of clear-cut supporting evidence for chemical carcinogenesis resulting from an occupational exposure.[2] Since Percival Pott's work, there have been thousands of epidemiologic investigations into occupational hazards—ranging from chemical exposures to ergonomic and organizational factors such as shift work—that have resulted in the creation of numerous agencies, such as the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH), with the mission to implement regulations to control hazardous exposures on the job and to protect the health and safety of workers.

Despite this, occupational exposures still have a profound impact on worker health. Although declining with time, there were nearly 2.9 million nonfatal workplace injuries and illnesses reported by private industry employers in the United States in 2015, a rate of 3.0 cases per 100 equivalent full-time workers.[3] In the public sector, an estimated 752,000 injury and illnesses were reported in 2015 from the nearly 18.4 million state and local government workers, resulting in a rate of 5.1 cases per 100 full-time workers; this is relatively unchanged from the

previous year (5.0 cases) but is notably higher than the rate among private industry workers, likely explained by differential reporting between these sectors and a larger proportion of high-risk jobs in the public sector, like policing and firefighting.[3]

In the United States, there were also 4,826 fatal occupational injuries in 2015, a rate of 3.4 per 100,000 full-time equivalent workers; this is a notable decrease from a rate of 4.2 in 2006, but it has remained relatively stable since 2009.[4] Globally, an estimated 2.3 million deaths in 2014 were attributed to occupation—approximately 2 million of which were due to work-related diseases while the remainder were due to occupational injuries.[5] Together, cardiovascular (circulatory) diseases and cancers were responsible for more than two-thirds of work-related deaths,[5] which demonstrates the importance of studying and identifying chronic occupational exposures, as chronic non-infectious diseases are the main long-term consequences of an unhealthy work environment.

The perceived risk of occupational injury or illness is in stark contrast to its actual risk; many underestimate the mundane tasks associated with their occupation, but it is often ordinary job requirements that, over time, can lead to harmful outcomes.[6] This highlights the need for occupational epidemiology in discovering and quantifying work-related hazards and disseminating findings to both the public and the appropriate agencies—like OSHA or NIOSH—that are designed to minimize risk through regulations, training, consultations, enforcement, and guidelines that advocate a healthy working environment.

This dissertation will focus on three different projects in the realm of occupational epidemiology. The first examines the relationship between occupational physical activity (OPA) and cerebrovascular disease (i.e., stroke and transient ischemic attack [TIA]) in older women. The second project explores the relationship between parental occupational exposure to livestock

around pregnancy and the risk of childhood cancer in offspring, while the third investigates parental occupational exposures, assessed via job exposure matrices (JEMs) and job titles, and the risk of childhood germ cell tumors (GCTs) in offspring. Although distinct, these projects are complementary exercises in occupational epidemiology that seek to identify and quantify the risks associated with occupational exposures in vulnerable populations.

1.1.1 Vulnerable populations

By investigating occupational exposures in older women, pregnant women, and children, this dissertation is focused on identifying risk factors in vulnerable populations. The study on OPA and cerebrovascular disease in women inherently address a primary research priority outlined by the National Occupational Research Agenda (NORA) in their 2002 publication, "The Changing Organization of Work and the Safety and Health of Working People." This publication noted that more research was needed to examine the effect of organizational stressors that are specific to women and older workers, as they may be disproportionally exposed to certain occupational risks.[7] The Sister Study, which will be the cohort utilized in the analysis of OPA and cerebrovascular disease, is comprised solely of women, 52% of whom were over the age of 55 at baseline, making it a suitable cohort to examine occupational risk factors for chronic cerebrovascular diseases in this vulnerable and understudied older female population. Similarly, the projects on parental occupation and childhood cancer address NORA research priorities by focusing on pregnant women. Due to the inherent nature of their condition and elevated sensitivity of the developing fetus to environmental toxins, pregnant women represent a particularly vulnerable and understudied population in the workforce.

1.2 Cerebrovascular disease

Using the World Health Organization (WHO)'s diagnostic criteria, stroke is a type of cerebrovascular disease classically defined as "rapidly developing clinical signs [symptoms[8]] of focal (at times, global) disturbances of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin."[9] There are three subtypes of stroke: ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. Ischemic strokes are marked by the obstruction of a blood vessel due to a blood clot or (typically atherosclerotic) plaque production, while hemorrhagic strokes occur when a blood vessel in the brain ruptures and bleeds; both result in a lack of oxygen and nutrients to the brain, causing cell death.[10] Intracerebral and subarachnoid hemorrhage differ based on the location of the ruptured vessel: the former denotes a rupture inside the brain, while the latter indicates a bleed just outside the brain, in the subarachnoid space. Both lead to compression of affected brain regions with symptoms similar to ischemic stroke. While the WHO's definition of stroke is commonly accepted in the epidemiologic literature, it does not account for transient ischemic attacks (TIAs), also known as "mini-strokes," which refer to a "brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour [but up to <24 hours[10]] and without evidence of acute infarction."[11] TIAs are similar to ischemic strokes insofar as they are caused by a blood clot, but the clot is only temporary and TIAs do not usually result in permanent brain damage, whereas stroke is likely to.[10]

Stroke—when considered separately from all other cardiovascular diseases—ranks fifth among all causes of death in the United States and is the leading cause of long-term disability.[12] According to the most recent statistics, 7.2 million individuals aged 20 or older self-reported having had a stroke; prevalence increases with age for both sexes and is known to vary by

race/ethnicity.[12] According to the CDC, 2.5% of non-Hispanic whites aged 18 or older have a history of stroke compared to 4.5% of non-Hispanic blacks, 1.8% of Asian/Pacific Islanders, 2.4% of Hispanics (of any race), 5.4% of American Indian/Alaska Natives, and 4.7% of other races or multiracial people.[13] Of all strokes, 87% are ischemic and 13% are hemorrhagic, of the latter, 10% are intracerebral and 3% subarachnoid. Each year, approximately 795,000 people experience a stroke—about 610,000 of these are first attacks and the remaining 185,000 are recurrent attacks.[12] According to recent statistics, TIAs are less prevalent than stroke, affecting about 5 million people in the United States; however, prevalence is suspected to be greater as many patients who experience symptoms consistent with a TIA fail to report it to their healthcare provider.[14] The incidence of TIA increases with age and varies by sex and race/ethnicity, with men, blacks, and Mexican Americans showing higher rates of TIA than their female and non-Hispanic white counterparts.[15, 16] Around 15% of all strokes are heralded by a TIA, and TIAs confer a substantial short- and long-term risk of stroke, hospitalization for cardiovascular events, and death.[17, 18]

1.2.1 Risk factors for cerebrovascular disease

Several risk factors for cerebrovascular disease have been well established in the literature, many of which are elements of an unhealthy lifestyle that elevate individual risk for a variety of diseases, such as CVD; these risk factors include hypertension, smoking, high cholesterol, heavy alcohol consumption, and obesity.[10, 19] However, it has been shown that elements of a healthy lifestyle—like diet high in fish, grains, fruits and vegetables or being physically active during leisure time—can reduce stroke risk.[20, 21] Previous cardiac events and other comorbidities, such as migraine or type-II diabetes, have also been shown to increase the risk of stroke.[10, 22] The most common cardiac precursor to stroke is atrial fibrillation, which

causes the heart to quiver and beat irregularly; this can result in an inefficient heartbeat that leaves residual blood in the atria, where it can pool, clot, and eventually result in an embolism, leading to ischemic stroke.[10] Other cardiovascular conditions, like coronary heart disease (such as angina and myocardial infarction), atherosclerosis, aneurysms, and comorbidities such as obesity, diabetes, and dyslipidemia similarly raise an individual's risk for stroke.[10]

Psychosocial factors such as stress and depression have been shown to increase stroke risk, especially in women. A recent meta-analysis of ten prospective cohort studies and four case-control studies found that those who reported general or work stress and/or stressful life events (i.e., death of a family member) were at an increased risk for stroke compared to those who did not report any types of stress (HR=1.33; 95% CI=1.17, 1.50).[23] There was an increased risk across stroke subtypes, but the risk was more pronounced for hemorrhagic stroke (HR=1.73; 95% CI=1.33, 2.25) than it was for ischemic stroke (HR=1.40; 95% CI=1.00, 1.97). The meta-analysis also revealed stark differences by sex, with stress impacting stroke risk in women (HR=1.90; 95% CI=1.40, 2.56) significantly more than men (HR=1.24; 95% CI=1.13, 1.36). However, there is no clear explanation for this difference between sexes and is uncertain whether these results indicate that women experience higher levels of stress, are more likely to report stress, or if perceptions of stress are different between men and women.[23] Regardless, the results of this meta-analysis are in agreement with a literature review of work-related stress among women—suggesting that work stress and job strain may be more powerful predictors of stroke risk in women than in men.[24]

Stress is not the only psychosocial factor to influence stroke risk; a recent study of incident stroke in women found that those who reported a history of depression, antidepressant medication use, a current depression diagnosis, and a low Mental Health Index score were all at

an increased risk of stroke. However, for each cycle they collected information, those who reported current depression were at a higher risk for stroke (HR=1.41; 95% CI=1.18, 1.67) than were those only reported a history of depression (HR=1.23; 95% CI=0.97, 1.56), compared with women who never reported a depression diagnosis or antidepressant medication use.[25] The mechanisms to explain an increased risk of stroke for psychosocial stress and depression have yet to be fully elucidated. Potential mechanisms involve the impact of perceived stress on vascular inflammation or oxidative stress, key elements of the basic pathophysiology of vascular disease.[23, 26] Objective stressors also contribute to disease risk, perhaps even more than perceived stressors; one study of San Francisco transit operators found that hypertension risk was higher among those who did not perceive observed stressors compared with those who perceived and report the same job stressors.[27] Stress may also increase catecholamine release and sympathetic activation, which may directly or indirectly affect the vascular system through increases in heart rate or blood pressure, thickening of the intima media of arterial vessel walls, or advancing carotid arterial disease.[26, 28] Depression may influence stroke risk directly through neuroendocrine, immunological, or inflammatory pathways,[29, 30] or indirectly through its association with unhealthy behaviors, like smoking, inactivity, and obesity.[31]

There are some suspected occupational risk factors for stroke in addition to work-related stress, but literature in the field is sparse. Occupational noise exposure has been positively associated with stroke incidence and intracerebral hemorrhagic stroke mortality in some studies,[32, 33] but other reports have not corroborated these findings.[34] There is also mixed evidence regarding occupational exposure to particles and stroke risk. Two studies reported positive associations between stroke risk or mortality and aluminum potroom workers and army cooks,[35, 36] occupations which indicate potential particle exposure; however, a more recent

analysis did not find similar results.[37] Yet, a subsequent study found a positive association between occupational exposure to both small (<1μm) and large (>1μm) particles and ischemic stroke; associations were stronger for persons exposed for at least five years compared with those who were ever exposed.[38] There has been no evidence to link agricultural exposures with stroke risk.[39]

A recent, multi-country case-control study investigated the impact of ten established risk/protective factors (i.e., hypertension, smoking status, waist-to-hip ratio, diet risk score, regular physical activity, alcohol intake, psychosocial factors, diabetes status, cardiac causes, and the ratio of apolipoproteins B to A1) on stroke risk by calculating population attributable risks (PARs), finding that they account for about 90% of the risk of stroke. However, the extent to which each factor accounted for stroke risk was dependent on the subtype; for example, the PAR for self-reported hypertension was 44.5% for intracerebral hemorrhage, but 31.5% for ischemic stroke. However, the direction of each risk factor (i.e., positive or negative) was consistent across subtypes.[19] While these findings appear to indicate that risk factors for stroke are well-known, it is important to note that PARs of different risk factors are not limited to a sum total of 100% and there is infinite room for additional risks. Recent evidence also suggests that some established risk factors require a deeper investigation. For example, while general physical activity was a risk factor mentioned in the review cited above, the authors did not collect or evaluate any data specifically on OPA. The failure to differentiate between occupational and leisure time physical activity may be problematic because recent evidence suggests these two types of physical activity may have opposite effects on CVD outcomes.[21, 40, 41] While the risk factors listed by the reviewers are generally in agreement with decades of research into factors that influence stroke

risk, research has yet to investigate the specific role of occupational risk factors including an examination of potentially paradoxical health effects of OPA and LTPA.

1.2.2 The physical activity health paradox

Physical activity has a profound impact on health and the hazards associated with a sedentary lifestyle are well-documented.[42-44] However, the term "physical activity" is vague and may involve leisure-time physical activities (i.e., exercise, sports, hobbies), commuting physical activities (i.e., walking, cycling), household chores, and/or occupational physical activities. Until recently, all domains of physical activity have been considered to confer similar health-promoting benefits,[45, 46] and current World Health Organization (WHO) recommendations regarding physical activity do not distinguish between LTPA and OPA.[47] However, prospective cohort studies report conflicting findings regarding the benefits of OPA: some studies show that high OPA is associated with improved health,[40, 48, 49] while others demonstrate that high OPA impairs health,[50-52] and a recent review of the newer literature concludes that high levels of OPA are associated with a 24% increased risk of CVD, while high levels of LTPA are associated with a 24% decrease in CVD.[53] The phenomenon of such differential effects of different types of physical activity has been called the "physical activity health paradox."[54, 55]

A potential biological explanation for the contrasting effects of LTPA and OPA lies in differential blood pressure responses to physical activity.[41] Elevated systolic blood pressure is an established risk factor for CVD,[56] and daily measurements of blood pressure have been shown to predict cardiovascular events.[57] Furthermore, physical activity plays an important role in the daily variations in blood pressure;[58, 59] LTPA like cycling and walking has been shown to reduce blood pressure,[60] but OPA like lifting and carrying heavy objects is known to significantly raise blood pressure in the short- and long-term.[41, 61] Therefore different effects on systolic blood

pressure may explain the differential impacts of LTPA and OPA on CVD health. However, another biological factor of interest is heart rate; elevated resting and average 24-hour heart rate, which is a known independent risk factor for CVD.[62-64] High OPA over extended periods of time has been shown to increase 24-hour heart rate, an association not observed with shorter duration high levels of LTPA.[65] For instance, the Belgian Physical Fitness Study reported a more than 3-fold increased all-cause mortality risk among working men in the upper tertile of ambulatory 24-hour heart rate (HR=3.21; 95% CI=1.22-8.44).[66] Yet, there are other aspects of OPA and LTPA that can contribute to differential disease risk.

Structurally, the nature of OPA is different from LTPA, which may lead to poorer CVD outcomes through increased worker stress and fatigue. Participation in LTPA is voluntary and the participant is generally in complete control of their actions, including how much to do and when and how long to rest. Conversely, OPA is an employment requirement and usually performed with little worker input: employees do not typically have control over work tasks, work hours, work speed, and other psychosocial, organizational, or ergonomic stressors that may be present in the work environment and determine the type, intensity, and duration of OPA. OPA is typically performed for longer time periods than LTPA and with less recovery time between and after activities. In addition to the biologic effects mentioned previously, this can result in exhaustion and fatigue, which has been associated with an increase in CVD and stroke.[67-69] Taken together, these biologic and structural differences between OPA and LTPA help explain the physical activity health paradox.

1.3 Childhood cancer

Childhood cancers are rare diseases with relatively unknown etiology. Approximately 10% of all pediatric cancers can be attributed to inherited genetic traits, while *de novo* somatic

mutations account for the remaining 90%.[70] As a result, many childhood cancers are thought to originate prenatally or from early childhood exposures. The developmental origin of health and disease (DOHaD) hypothesis is used to support the notion that some childhood cancers have a prenatal origin; this hypothesis emerged nearly 30 years ago after epidemiologists found high correlations between birthweight and rates of adult death from ischemic heart disease.[71] The DOHaD hypothesis suggested that the fetus's adaptation to the intrauterine environment (i.e., undernutrition) resulted in permanent fetal programming that shaped the body's structure, function, and metabolism—in addition to contributing to adult disease.[72] While this theory first applied to adult CVD, it has also been extended to the study of adult cancers and other chronic diseases; however, it has not explicitly examined with respect to childhood cancer. Nevertheless, it can be used to support the notion that prenatal exposures can affect long-term disease risk. There is some evidence for the prenatal origin of pediatric cancer; these cancers commonly co-occur with congenital malformations, and prenatal factors like birthweight have been consistently associated with cancer risk in children, for some cancer types.[73-76] Furthermore, some childhood cancer cells possess embryonal features;[77] however, it is not yet known whether these cancers arise from embryonal cells *in utero* or as a consequence of a single oncogenic event in a more mature prenatal cell.[78] While biological pathways have not yet been fully elucidated, epigenetic events involving DNA methylation and hormonal signaling via the placenta are likely mechanisms related to carcinogenesis.[79-82]

In the United States, there are approximately 15,700 incident cancers diagnosed annually among individuals aged <20 years.[65, 83] There are several different types of childhood cancers, but leukemias and CNS tumors are the most commonly diagnosed.[84] The incidence rate of all pediatric cancers in the United States has been slightly increasing at an annual rate of 0.6% since

1975.[84] While incidence may be increasing, mortality has substantially declined with time; despite this, childhood cancer remains the leading cause of death by disease among children in the United States.[84] Worldwide, an estimated 163,300 new childhood cancer cases occurred among children 0-14 years of age in 2012, with an estimated 80,000 deaths; similar to the U.S., global mortality has been declining over the past 40 years, but more developed countries have been experiencing an increase in incidence rates since the 1970s.[85] Reasons for these trends are largely unknown but may be in part to improved diagnosis and reporting methods; trends in developing countries are difficult to capture due to inadequate reporting and a small amount of resources.

1.3.1 Risk factors for childhood cancer

There are few established risk factors for childhood cancer, likely due to their rarity. Genetic risk factors explain 5-10% of all childhood cancer cases, leaving the remaining 90% with mostly unknown etiology.[75] Demographic risk factors impact the distribution of childhood cancer cases in the population: non-Hispanic white children and boys are more likely to be diagnosed with cancer in childhood, but age at diagnosis is largely determined by tumor histology; for example, acute lymphoblastic leukemia (ALL) is known for its peak incidence at 2-5 years old, whereas bone sarcoma incidence peaks in adolescence.[75] Ionizing radiation and prior chemotherapy are among the few established risk factors for childhood cancer, with few other environmental factors have been causally linked to childhood cancer development.[75, 86, 87] Intrinsic risk factors for childhood cancers—like birthweight, parental age, and congenital anomalies—have been well established in the literature. The risk of several cancers, such as ALL[88] and CNS tumors,[89] has been shown to rise as linear function of birthweight, while others, like neuroblastoma,[90] have been associated with low birthweight. Other cancers, like acute

myeloid leukemia, show a U-shaped relationship with birthweight.[75] Congenital malformations have also been consistently associated with childhood cancer risk.[73, 74] Some congenital anomalies, like Down syndrome, have been clearly linked to a specific childhood cancer (in this instance, ALL),[91] but due to the rarity of both individual birth defects and individual childhood cancers, specific associations have not yet been full elucidated for all congenital malformations and cancer types.

1.3.2 Infection and childhood cancer

Exposure to infection (either *in utero* or after birth) has been investigated in the etiology of several childhood cancers, though most studies focus on leukemia and brain tumors.[92-97] Two competing hypotheses exist for the role of infection in childhood cancer development; Greaves's views infection as conferring protection against cancer,[98] while Kinlen's suggests exposure to infection *in utero* or in early life increases cancer risk.[99] While these hypotheses were originally developed to investigate increasing leukemia rates, they are now thought to be possible for many cancers. Greaves's "delayed infection" hypothesis asserts that exposure to infections in early life primes the immune system and confers protection against cancer development later in life, while those who don't have early life exposure to infections are at an increased risk of cancer development. Conversely, Kinlen's "population mixing" hypothesis claims that cancers like leukemia have an infective origin due to unusual population mixing; for example, people who live in geographically isolated areas may elude exposure to common infective agents—to these groups, "incomers" can introduce infective agents that result in dramatic consequences. Kinlen views leukemia as one of these consequences, arising as a result of a rare, abnormal immune response to infection.[99-101] Kinlen has used evidence from isolated nuclear reprocessing plants in Britain to support this notion; in his studies, he showed that there was an excess number of

childhood leukemia cases after an influx of "incomers" to the area, whom he theorizes were responsible for localized epidemics due to increased contact between susceptible (i.e., those who were already living in the isolated are) and infected (i.e., "incomers") individuals.[100, 102, 103] While these hypotheses have increased research interest in infection and childhood cancer, specifically childhood leukemia,[93, 95, 104-106] no studies have yet to identify a specific infectious agent relevant to the etiology of childhood leukemia. Some cancers, however, do have an established viral cause: Burkitt's lymphoma and Epstein-Barr virus; liver cancer and Hepatitis B and C viruses; cervical cancer and human papillomavirus; and Kaposi's sarcoma and human herpesvirus-8 and Kaposi's sarcoma herpesvirus.[107, 108]

While not all cancers have an established viral cause, infectious agents are suspected in the etiology of many neoplasms, including childhood brain tumors. Studies have shown that viruses can cause brain tumors in animals,[109-112] but evidence for an association with humans is less conclusive. Nevertheless, one study has reported a positive association between prior *Toxoplasma gondii* infection and gliomas in adults,[113] while others have suggested associations between maternal infection during pregnancy and childhood brain tumor risk in offspring.[94, 97, 114] Furthermore, there is evidence to suggest that infections may only be relevant to the etiology of certain brain tumor subtypes. For example, JC polyomavirus has been widely studied as a candidate etiologic agent for CNS tumors because it has been shown to induce brain tumors in animal models[111, 112] and has been detected in pediatric and adult CNS tumor subtypes with varied frequencies.[115] However, studies have generally reported a high prevalence in glial tumors and low to no prevalence in medulloblastomas,[116-118] bolstering the idea that infections are only pertinent to certain histologic subtypes of brain tumors.

Rarer childhood cancers have been less frequently examined with respect to infection and these studies tend to yield mixed results. Few studies have assessed the role of infection in the etiology of childhood rhabdomyosarcoma, a malignant tumor of developing skeletal muscle. One study found no association between infection and rhabdomyosarcoma, but detected positive associations between incomplete immunization schedules and cancer risk.[119] These findings corroborate the results of previous study based on 33 rhabdomyosarcoma cases that detected inverse associations with complete immunization schedules and cancer risk.[120] Another study from the Children's Oncology Group reported inverse associations between rhabdomyosarcoma and allergies and hives, suggesting that atopic exposures in early life alter the immune system and protect against cancer development later in life.[121, 122] This report also estimated inverse associations between rhabdomyosarcoma, day care attendance, and breastfeeding for more than one year, further suggesting immune system development has a role in tumor onset.

The literature is mixed with respect to infection's role in the development of neuroblastoma. An English cohort study of 266,710 live births in Cumbria from 1950-1991 found an increased risk of neuroblastoma among the children of "incomers" (i.e., children of parents who were both born outside the study area),[123] a proxy for population mixing; however, a later study from Northern England could not corroborate these findings, though it only included birth 1975-1994 and excluded the county of Cumbria in its study population.[124] A South Korean ecologic study reported a temporal correlation between neuroblastoma diagnoses and recent human parainfluenza virus, but this study design limits the generalizability of their findings.[125] Alternatively, a case-control study of 538 neuroblastoma cases estimated an inverse association between select childhood infections (e.g., chickenpox, mumps, and measles), day care attendance, and neuroblastoma risk, but noted that positive associations were observed for other

childhood infections, like ear infection.[126] These mixed results suggest a need for more research in the area.

Few studies have investigated infection in the etiology of Wilms tumor. However, a report from the Children's Oncology Group estimated an inverse association between Wilms tumor and breastfeeding; while there is no clear mechanism to explain this association, the authors noted that breast milk contains agents that can protect against infection or potentially carcinogenic agents.[127] Evidence for an association with maternal infection during pregnancy is less clear: A case-control study of 202 Wilms tumor cases revealed an increased risk of tumor development among the children of mothers who reported a vaginal infection in pregnancy,[128] but a later study of the same size could not corroborate these findings.[129]

There is little evidence suggesting infection plays a role in the etiology of childhood bone tumors, however there are few studies on these rare tumors. An Austrian case-control study of juvenile bone tumors found positive associations between tumor development and history of measles and mumps, but an inverse association with a history of chickenpox and dermal/respiratory allergies.[130] This report also found an inverse association between breastfeeding and bone tumor risk in boys, but other studies have not been able to link breastfeeding and childhood bone tumors.[131] Other studies have reported positive associations between parental farming exposures and both Ewing's sarcoma and osteosarcoma in offspring,[132-135] but these studies did not distinguish between livestock and crop work, making it difficult to identify the most relevant exposure.

1.4 Childhood germ cell tumors

Childhood GCTs are an assorted group of malignant and benign neoplasms that are believed to originate from primordial germ cells, but vary with respect to their clinical

presentation, histopathology, and biologic characteristics.[76, 136, 137] GCTs in children under 15 are rare, comprising only 3.5% of all pediatric cancers.[138] In the United States, the incidence rate of GCTs for children <15 is approximately 6.0 per million,[139] while in Europe it is estimated to be 4.8 per million.[140] In young children, there are two common subtypes of GCTs: yolk sac tumors and teratomas.[141] While few studies have stratified by histologic subtype, some evidence suggests these subtypes have distinct etiologies and ages at diagnosis, as well as heterogenous tumor DNA methylation signatures.[76, 141-145]

1.4.1 Risk factors for childhood germ cell tumors

Likely due to their rarity, the etiology of childhood GCTs is largely unknown; however, studies have reported consistent positive associations between cancer incidence and Asian/Pacific Islander race, abnormal fetal growth, birth defects like cryptorchidism, and congenital malformations.[76, 146-150] Increasing maternal age has been positively associated with childhood GCT risk in several studies,[146, 151, 152] but there has been inconsistent evidence with respect to other maternal factors. One study reported a decreased risk of GCTs in mothers who had a diet high in fruits and vegetables during pregnancy,[153] but this association was only pertinent to male offspring. Another study reported maternal vitamin supplementation to be inversely associated with GCT risk in offspring;[145] however, a stratified analysis revealed this association to be null for yolk sac tumors. Prolonged breastfeeding (> 12 months) was positively associated with cancer risk in a study of 105 childhood GCT cases,[154] but a more recent analysis with double the sample size failed to corroborate these findings.[155] Parental drinking has not been linked with GCT risk in offspring.[156] The role of smoking is less clear; an exploratory analysis revealed no association between paternal smoking and GCT risk in children, but estimated an inverse association between cancer risk and the number of cigarettes smoked by the

mother during pregnancy, which the authors credited to differences in recall.[154] Other studies have not been able to elucidate a clear relationship between parental smoking and childhood GCT risk.[156-159] No studies have found an association between exposure to female hormones *in utero* or fertility treatment and childhood GCT risk.[151, 160]

Several studies have found that both high and low birthweight are positively associated with GCT risk. A registry-based study of 152 childhood testicular GCT cases <15 years revealed a U-shaped relationship between birth weight and cancer incidence, finding increased risks among children with high (>4000g) and low (<2500g) birth weight. When the authors used the Ponderal index (birth weight divided by the cubed value of birth length) to classify growth, a similar U-shaped relationship was observed.[146] While findings for high birth weight have been corroborated by other studies,[154, 156, 160] a recent analysis found that an initially observed positive association between low birth weight (and low gestational age) and GCT risk became null after excluding cases diagnosed within 5 days of birth.[76] This study only observed an association for low birth weight with teratomas and credited it to reverse causation; that is, the teratoma was likely the reason for early, presumably induced, delivery—and therefore low birth weight—as teratomas are increasingly diagnosed *in utero*.[161]

The relationship between socioeconomic status (SES) and GCT risk is unclear. A population-based study of four Scandinavian countries reported an increased risk of GCTs with lower levels of maternal education[146] and these results were consistent with a population-based study of young California children.[76] However, a pooled population-based analysis of five US states (including California births over a nine-year period) did not find an association between childhood GCTs and maternal education.[162] Conversely, a nationwide study in the United States

reported a lower risk of childhood GCTs in higher-poverty areas; however, poverty metrics were on the county-level, making it difficult to compare with individual measures of SES.[163]

Few studies have investigated parental occupational exposures in the etiology of childhood GCTs. These studies have reported positive associations between parental occupational exposure to chemicals or solvents (maternal odds ratio [OR]=4.6; 95% CI=1.9, 11.3; paternal OR=2.2; 95% CI=1.1, 4.7) and plastic/resin fumes (maternal OR=12.0; 95% CI=1.9, 75.0; paternal OR=2.5; 95% CI=1.0, 6.5) and childhood GCT risk in offspring;[154] however, results were mixed or null for other occupational exposures, such as exhaust fumes, radiation, dyes, and farm animals.[154, 158] Both occupational and non-occupational studies have been unable to link parental pesticide exposure and childhood GCT risk.[143, 155, 164] Non-occupational studies of certain chemicals have shown conflicting results with respect to *in utero* or early life exposure and childhood GCT risk. One recent analysis found that ambient exposure to dichloromethane (a solvent often used in paint removers and other chemical processes) during pregnancy and the first year of life was positively associated with childhood GCTs, particularly teratomas.[165] Another study estimated a weak positive association between traffic-related air pollution in pregnancy and childhood GCT risk, mostly for teratomas.[144] Similarly, a Spanish case-control study estimated an imprecise but positive effect for childhood GCTs and proximity to urban areas with traffic pollution.[166] However, other case-control studies were unable to corroborate these findings.[154, 155, 167]

While family history of testicular cancer is an established risk factor for adult testicular GCT development,[168] the role of family history of cancer in the etiology of childhood GCTs is less clear.[154, 158, 169, 170] One study reported an increased risk of malignant GCTs in children who had a first-degree relative with cancer,[154] but other studies did not corroborate this finding.[158, 170]

A more recent study could not find an association between GCT risk and family history of cancer overall, but reported that a family history of cancer with onset <40 years was associated with an increased risk of GCTs in males, but a reduced risk of cancer in females. Similarly, they found a positive association between family history of melanoma and cancer development in males, but an inverse association between family history of ovarian or uterine cancers and GCT development in girls.[169] Evidence has been mixed with respect to whether GCTs are a part of Li-Fraumeni syndrome.[171, 172]

1.5 Occupational exposures and childhood cancer

Parental occupational exposures have been frequently examined in the etiology of childhood cancer; however, there is no well-established theory for the biological mechanisms by which these exposures would impact cancer risk in offspring. Nevertheless, there is evidence to suggest that exposures during preconception, pregnancy, and after birth may be relevant to the etiology of childhood cancer, though mechanisms differ by the timeframe of interest.

1.5.1 Preconception

Preconception exposures are intended to capture the period of spermatogenesis, the process by which new sperm cells are created; it can take between 74-120 days until they are fully matured in the epididymis, during which time developing cells are susceptible to factors like oxidative stress, which has the potential to alter paternal DNA.[173-175] Studies in rats have shown that exposure to toluene, an organic solvent used in many industries and commercial products, directly induced oxidative DNA damage to spermatozoa.[176] Furthermore, studies in humans have shown occupational noise and heat exposure, as well as exposure to polycyclic aromatic hydrocarbons, to be associated with DNA damage and fragmentation in sperm.[177, 178]

Exposures that result in sperm damage have the potential to create germline mutations that are passed on to children and contribute to carcinogenesis. While several studies have identified agents that induce oxidative DNA damage in sperm, no mutagens or carcinogens have been identified in the etiology of childhood cancer in paternal offspring.

1.5.2 Pregnancy

In utero occupational exposures have been frequently examined in the etiology of childhood cancers and are rooted in the idea that changes to the prenatal environment lead to altered fetal programming, resulting in permanent changes that affect long-term disease risk.[71, 80, 179] It is well-established that certain agents can cross the placenta and expose the developing fetus, but few agents have been identified as causing cancer in offspring with the exception of diethylstilbestrol, a synthetic form of estrogen that was prescribed to women in the mid-1900s to prevent miscarriage.[180-182] This is perhaps the most notorious case of *in utero* exposure and cancer in offspring, but researchers have continued to examine other maternal exposures during pregnancy in order to assess their impact on offspring health, including cancer development. Most studies of maternal occupational exposures and childhood cancers examine the risk of leukemias and brain tumors, but studies of rarer childhood cancers are sparse.[183]

1.5.3 After birth

Parental occupational exposures after birth have been investigated in few studies of childhood cancer, most of which examine exposures such as pesticides or infectious agents. For agents like pesticides and dusts, exposure residues can be brought home by parents from clothing or skin and transferred to children directly or through buildup of dusts in the home or in vehicles.[184, 185] Parents who work in occupations that include a high risk of infection, such as

daycare workers[186, 187] or livestock farmers,[188-190] also have the potential to expose their children at home. One study of hog operation workers found that family members of infected workers were likely to experience the same infection,[191] while other studies have supported the role of household networks in disease transmission.[192] These post-birth exposures have the potential to cause cancer in children through mechanisms described previously.

1.6 Lifestyle characteristics of relevant occupations

As this dissertation utilizes occupational data from Danish populations, it is important to note the differential rates of certain lifestyle characteristics (e.g., smoking) across relevant Danish occupations. Specifically, within the farming industry smoking rates differ by the type of product farmed. A 1988 study based on survey responses from 1,175 farmers (70% response rate) indicated that smoking was more prevalent among dairy farmers (41.9%) and dairy/pig farmers (37.1%) than only pig farmers (35.7%) or non-livestock farmers (35.1%).[193] More recent evidence has shown that the prevalence of smoking among female farmers is lower than that of other female workers (15% vs. 25%).[194] However, smoking rates for other occupations within the farming industry, like butchers and slaughterhouse workers, have been noted to be higher than the smoking rates for other Danish occupations.[195, 196] Overall smoking prevalence in Denmark has decreased over time;[197] however, the smallest reductions were observed among women and those with low educational attainment. With respect to alcohol consumption, one study found that female farmers were more likely to be nondrinkers (57.9%) than controls (53.8%);[194] however, information on other lifestyle characteristics in the Danish working population is sparse.

1.7 Objective

In this dissertation, we will investigate the role of various occupational exposures and their influence on the health outcomes in certain vulnerable populations. Specifically, we will examine the impact of exposure to OPA and the 6-year incidence of stroke and TIA in a cohort of older working women; parental occupational exposure to livestock or animal dust and the risk of childhood cancers in offspring; and the role of parental occupational exposures, assessed via JEMs and job titles, and the risk of childhood GCTs in offspring.

Chapter 2. Occupational physical activity and 6-year incidence of stroke and transient ischemic attack in women

2.1 Abstract

Recent evidence suggests leisure time physical activity (LTPA) is beneficial to cardiovascular health, but occupational physical activity (OPA) is detrimental; however, data on OPA and cerebrovascular disease are limited. This study aims to assess the relationship between OPA, stroke, and transient ischemic attack (TIA) in a cohort of US women. Information on OPA (current job, longest held job, and cumulatively for all jobs held since age 18) and lifestyle factors was assessed via interviews at enrollment for 31,270 Sister Study participants aged 30-74 years and employed at baseline. OPA was assessed in 4-6 categories ranked by intensity (mostly sitting, sitting/standing equally, mostly standing, continuous walking/movement, and two levels of heavy physical labor); the highest three OPA levels were combined and labeled "mostly dynamic work." Associations between OPA and incident cerebrovascular disease during an average follow-up of six years were assessed in Cox proportional hazard regression models adjusted for socio-demographic, biological, and behavioral factors including LTPA. In this study, 715 incident diagnoses of stroke (n=441) and TIA (n=274) were reported by participants or next of kin. Compared to mostly sitting, mostly dynamic OPA at the current job was associated with an increased risk of TIA (hazard ratio [HR]=1.63; 95% confidence interval [CI]=1.07-2.48), while mostly dynamic OPA at the longest held job was associated with an increased risk of stroke (HR=1.45; 95% CI=1.06-1.97). Associations were stronger among women without cardiovascular disease or hypertension at baseline. The results of this comprehensive analysis suggest that mostly dynamic OPA is positively associated with incidence of stroke and TIA in women, further corroborating the notion of the physical activity health paradox.

2.2 Introduction

While stroke and TIA are relatively rare, stroke is among the leading causes of death and is the leading cause of long-term disability in the United States.[198] Stroke and TIA share a similar pathophysiology and are mostly distinguished by the duration of clinical symptoms; TIAs (also known as "mini-strokes") are acute, lasting <24 hours, while stroke symptoms last for 24 hours or more and can lead to permanent disability or death.[11, 199] Like cardiovascular disease (CVD), stroke occurrence is associated with socio-demographic, lifestyle, and environmental factors.[199] Racial and sex differences have been well-established;[198] although men have an overall higher risk of developing stroke, it is more prevalent in women because of their average longer lifespan.[198, 199]

Risk factors for stroke and TIA noted in the literature are mainly elements of an unhealthy lifestyle which elevate an individual's risk for a variety of diseases, such as CVD; these risk factors include hypertension, smoking, high cholesterol, heavy alcohol consumption, and obesity.[19, 199] In contrast, elements of a healthy lifestyle—like diet high in fish, grains, fruits and vegetables or participation in high levels of LTPA—have been associated with lower stroke risk.[20, 21, 200]

While LTPA is protective of cerebrovascular disease, the role of occupational physical activity (OPA) in the etiology of stroke and TIA is less clearly understood, especially in women. No studies have examined the relationship between OPA and TIA, and only a handful have examined stroke as an outcome,[21, 201-206] with fewer providing sex-specific results.[21, 203-206] In women, lower OPA jobs were generally associated with a higher risk of stroke;[21, 203-205] however, some studies did not have the statistical power to investigate higher levels of OPA.[204, 205] Furthermore, most of these studies relied on crude exposure assessment, categorizing OPA into

2-3 non-specific levels (e.g., low, moderate, and high) with arbitrary cut-points.[21, 201, 203, 204] In contrast, one study used a validated questionnaire to assess OPA[207] and found that, in women, stroke risk moderately increased with higher levels of OPA.[206] Only one study was able to examine a large number of stroke cases (n=1,366) and also adjusted for other types of physical activity (i.e., LTPA, commuting physical activity) when examining the OPA-stroke relationship, finding slightly protective effects of higher OPA on incident stroke risk in women.[21]

These older studies appear to conflict with recent reviews of the epidemiological literature that suggest paradoxical health effects for physical activity, with OPA being positively and LTPA being inversely related to CVD and mortality[53, 65, 208-210] or having no effect at all after adjustment for OPA.[51, 211, 212] A similar paradoxical effect was recently reported for Parkinson's disease, a neuro-degenerative disorder.[213]

The current study aimed to investigate the relationship between OPA and incident stroke and TIA, separately for current job, longest held job, and all jobs relying on a cumulative lifetime exposure measure. This analysis overcame several methodological limitations of previous studies by employing posture-based OPA exposure assessment, comprehensive adjustment for potentially confounding factors including LTPA, and use of a sufficiently large cohort of working women followed for an average of 6 years.

2.3 Methods

Study population. Subjects were participants in the Sister Study, a prospective cohort study originally designed to assess genetic and environmental risk factors for breast cancer (http://sisterstudy.niehs.nih.gov). Between 2003 and 2009, the Sister Study enrolled 50,884 women aged 30-74 who resided in the US or Puerto Rico and who were breast cancer-free at enrollment but had a sister with breast cancer. At baseline, written informed consent was

obtained and interviews were conducted. Women were excluded from the present analysis if they were unemployed or homemakers at enrollment (n=18,039) or if they did not report occupational physical activity for their current job (n=63); additionally, a vanguard group of women who completed a non-comparable version of the occupational questionnaire were excluded from analyses (n=1,512), resulting in an analytic cohort of 31,270 women. The Internal Review Boards at the National Institute of Environmental Health Sciences, Copernicus Group, and the University of California, Los Angeles approved the study.

Outcome assessment. Incident stroke and TIA cases were self-reported doctor's diagnoses reported on annual health follow-ups between 2005 and 2015. If a participant died prior to the annual health follow-up, next of kin were contacted to report any known diseases that were diagnosed over the previous follow-up period. Fatal cases were confirmed via the National Death Index and/or the individual's death certificate throughout follow-up. In this analysis, fatal and nonfatal cases are grouped together because there were few confirmed fatal cases of stroke (n=8) and no confirmed fatal cases of TIA. Reporting an event did not make participants ineligible for subsequent events, e.g., if a participant reported a TIA at the first follow up and a stroke at the second follow up, they were considered events in both analyses.

Assessment of occupational physical activity. At enrollment, study participants completed a computer-assisted telephone interview in which they were asked to report detailed information for all jobs, military service, and volunteer work performed after age 18 for at least 10 hours per week. For each job, participants were asked, "Which of the following best describes your usual physical activity while on the job?" The possible responses were: (1) mostly sitting, with some standing and/or walking; (2) sitting and standing equally (may include some walking); (3) mostly standing with some walking; (4) continuous walking or other movements that increase your heart

rate slightly; (5) heavy manual labor that causes sweating or increases your heart substantially; and (6) sporadic heavy manual labor. Due to small numbers, the latter two categories were collapsed in preliminary analyses into a group labeled "heavy manual labor." However, because there were still few events in this exposure group, it was further combined with "continuous walking or other movements" into a category labeled "mostly dynamic work," resulting in a four-level exposure variable for OPA: mostly sitting, sitting and standing equally, mostly standing, and mostly dynamic work. This report primarily uses the four-level OPA measure and separately assesses OPA for participants' current job and longest held job. Based on the entire reported life job history after age 18, a cumulative measure of high levels of OPA was created as the proportion of work years spent performing "mostly dynamic work" (0, >0-<0.25, 0.25-<0.50, 0.50-<0.75, and ≥0.75).

Selection of covariates. Potential confounders were identified using *a priori* knowledge and directed acyclic graphs, as well as change-in-estimate criteria. Traditional cardiovascular risk factors such as age, body mass index (BMI), smoking status, alcohol intake, and LTPA were selected for inclusion due to their strong influence on stroke risk[199] and association with OPA.[214] Work-related factors, like night work and discrimination at work, were selected for adjustment because they have been shown to increase CVD risk in other studies.[215, 216] Additionally, heart rate and systolic and diastolic blood pressure, which are known, independent hemodynamic risk factors for CVD,[56, 217, 218] were included for adjustment; however, these factors may also be considered potential mediators of the OPA-CVD relationship and therefore analyses were performed both with and without adjustment for these hemodynamic risk factors. In final analyses, we used the product of heart rate and pulse pressure (rate*pressure; where pulse pressure = systolic minus diastolic blood pressure) to adjust for these hemodynamic factors.

A variety of other covariates were assessed, but not used for adjustment in final statistical models. Socioeconomic factors including race/ethnicity, income, and education level were examined as potential confounders but not employed in final models because they did not change effect estimates by more than 5%. We created a simple sum diet score based on participants' responses to an extensive food frequency questionnaire, as well as a variable to indicate job strain as derived from a 17-item Job Content Questionnaire,[219] both of which were empirically found not to be confounders in exploratory analyses and therefore removed from our final adjustment sets. We assessed the role of both mistreatment/harassment at work and discrimination at work but chose to only adjust for the latter because it was a more inclusive measure and empirically more predictive of stroke risk. Additionally, we explored individual hemodynamic measures (e.g., heart rate or systolic and diastolic blood pressure, each alone instead of the combined rate pressure product) as potential confounders but did not include these variables in final models because our operationalization as one variable (i.e., rate pressure product) was empirically more predictive of stroke risk.

Assessment of behavioral factors. At baseline, LTPA was assessed using metabolic equivalent task (MET) hours per week in concordance with established guidelines.[220] Participants were asked to recall information on all sport/exercise activities performed during the last 12 months, including the number of hours spent per week on each activity. Weekly energy expenditures were determined using MET values for each activity. Each participant's LTPA was classified based on the World Health Organization (WHO) guidelines for adults: (1) at least 150 minutes of moderate-intensity physical activity (3-<6 METs) per week or (2) at least 75 minutes of vigorous physical activity (6+ METs) per week.[47] Those who met both requirements were classified in the latter category to reflect more dynamic LTPA. Women who participated in

moderate-intensity or vigorous LTPA, but not for the recommended amount of time per week, were classified as "insufficient activity time to meet requirements." Women who only participated in LTPA at MET values of <3 were categorized as such, as were study participants who did not partake in any LTPA. We also explored adjustment for LTPA by categorizing both raw and corrected MET values,[221] but chose not to employ these variables because WHO recommendation-based categories were empirically shown to better control confounding in exploratory analyses.

Information on lifetime smoking and alcohol consumption was ascertained per questionnaires at baseline. Participants were categorized into never smokers, former smokers, and current smokers. Detailed information on alcohol consumption habits over the past 12 months was collected and participants were categorized based on findings from the current alcohol-CVD literature:[222, 223] never drinkers, former drinkers, consuming <1-3 drinks/day, and consuming >3 drinks/day.

Assessment of anthropometric and hemodynamic factors. At the time of enrollment, current height, weight, heart rate, and systolic and diastolic blood pressure were measured during home or office visits by trained study personnel. Body mass index (BMI) was calculated as weight (kg)/height (m) squared and categorized according to WHO definitions: underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (30–34.9 kg/m^2), severely obese (35–39.9 kg/m^2) and morbidly obese (≥40 kg/m^2).

Blood pressure was measured by trained study personnel after participants sat and rested for a few minutes. Up to three sitting measurements of systolic and diastolic pressure were taken 1-2 minutes apart and a left-right-left protocol was used if both arms were available;[224] these measures were then averaged for analyses after checking for outliers. Blood pressure values

were considered to be outliers if systolic blood pressure was less than 80 mmHg or greater than 180 mmHg; if diastolic blood pressure was less than 40 mmHg or greater than 100 mmHg; or if large discrepancies existed between the systolic or diastolic blood pressure measures. After individual inspection of these data, three confirmed outliers were removed and the remaining values were averaged. Heart rate was measured by trained study personnel via palpation of the radial pulse for 1 full minute after participants were instructed to rest for at least 5 minutes. Heart rate values were considered to be outliers if they were less than 40 beats per minute or greater than 100 beats per minute. After individual inspection, two confirmed outliers were removed and set to missing.

We created values for pulse pressure, defined by the difference between systolic and diastolic pressure readings, and the rate pressure product, defined by the product of the pulse pressure and heart rate. Both measures have been shown to be independent predictors of CVD risk[225, 226] and were used to explore the role of hemodynamic factors when controlling for potential confounding.

Hypertension at baseline was assessed in multiple ways. During baseline questionnaires, participants were asked, “Has a doctor or other health professional ever told you that you had high blood pressure or hypertension, or that you had borderline high blood pressure other than during pregnancy?” If participants responded “yes” to either hypertension or borderline hypertension, they were asked whether or not they had ever taken medication for their high blood pressure. In the present analysis, participants were categorized as having hypertension if they self-reported a doctor’s diagnosis of hypertension, self-reported antihypertensive medication use, or had baseline blood pressure measurements that indicated hypertension (systolic blood pressure

≥135 and/or diastolic blood pressure ≥85) according to established clinical guidelines for at home measurements in effect at that time.[227]

Assessment of other covariates. Information on working night shifts was collected at baseline (ever vs. never). Discrimination at work was assessed in the first follow-up questionnaire dedicated to stress and coping topics (approximately one year after enrollment). Participants were separately asked if they had "ever been treated unfairly in job hiring, promotion or firing due to" their sex, age, race/ethnicity, sexual orientation, or illness/medical condition. If the participant had responded "yes" to any of these five questions, they were classified as ever experiencing discrimination at work.

Statistical analyses. Multivariable-adjusted Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the relationships between OPA and stroke or TIA, with days since study enrollment used as the timescale. In initial analyses, four levels of adjustment were explored: (1) age-adjusted only; (2) adjustment for age and behavioral factors (smoking, alcohol consumption, BMI, and LTPA); (3) adjustment for age, behavioral factors, and work-related factors (discrimination, night work); and (4) adjustment for age, behavioral factors, work-related factors, and potentially mediating hemodynamic factors (rate pressure product). All subsequent analyses are based on fully-adjusted models; supplementary analyses provide results without adjustment for the rate pressure product. For each model and covariate, the Cox proportionality assumption was assessed by examining the relationship between scaled Schoenfeld residuals and time; for any covariate that violated the proportionality assumption, an interaction term with time and the covariate was added to the model.[228]

Sensitivity analyses were performed with stratification by two baseline health characteristics: hypertension status and pre-existing cardiovascular disease status. Pre-existing

CVD was assessed by self-reported doctor's diagnosis of previous myocardial infarction, angina, congestive heart failure, arrhythmia, stroke, or TIA at baseline. We did not exclude those who reported a previous stroke or TIA at baseline because a previous cerebrovascular event does not exclude an individual from experiencing a subsequent event, but rather increases their risk of experiencing such an event.[199] A further sensitivity analysis, stratified CVD into coronary heart disease (angina, myocardial infarction) versus the remaining CVD listed; these analyses adjusted only for age due to small subsample sizes. All statistical analyses were conducted using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

2.4 Results

During an average of 5.7 (SD 2.3) years of follow-up, 441 incident stroke diagnoses and 274 incident TIA diagnoses were reported by participants or next of kin, resulting in incidence rates of 221 and 140 per 100,000 person-years, respectively. There were 148 cases where both a stroke and TIA were reported. Population characteristics, stratified by whether or not a cerebrovascular event was reported during follow-up, are shown in Table 1. Those with a cerebrovascular event during follow-up were older at baseline, more likely to be current smokers, but less likely to be current drinkers compared to event-free women. With respect to physical activity, those with a cerebrovascular event less likely to participate in any LTPA, more likely to report OPA involving continuous walking/movements for both current and longest held job, and more likely to ever work a job involving dynamic OPA compared to event-free women. Regarding other occupational characteristics, women without a cerebrovascular event during follow-up were less likely to ever work a night shift or ever face discrimination at work. All hemodynamic measures were higher among those who experienced a cerebrovascular event

during follow up compared to event-free women. Supplementary Table 2.1 shows population characteristics stratified by baseline CVD status.

Table 2.2 shows the associations of OPA level with stroke incidence in models with incremental adjustment for potential confounders (models 1-4), separately for current and longest held job. Compared with women who reported mostly sitting at their current job (the reference group), women who reported sitting and standing equally had a 15% higher risk of stroke (age-adjusted HR=1.15; 95% CI=0.91-1.45, model 1). Women who reported mostly dynamic work at their longest held job experienced a 55% higher risk of stroke compared with those who reported mostly sitting (age-adjusted HR=1.55; 95% CI=1.17-2.06). This association appeared to be driven by women who reported OPA as continuous walking or other movements that raised their heart rate slightly (age-adjusted HR=1.62; 95% CI=1.21-2.16), but not by women with heavy manual labor jobs (age-adjusted HR=1.03; 95% CI=0.43-2.51). Further adjustment for behavioral, work-related, and hemodynamic factors only slightly attenuated these risks.

Table 2.3 displays OPA effects on TIA incidence with incremental adjustment for confounders, separately for current and longest held job. Compared with women who reported mostly sitting at their current job, higher risks of TIA were observed for all other levels of OPA. Increasing physical workloads determined by the current job show a strong monotonic positive association with TIA incidence across OPA levels. For the longest held job, age-adjusted models show a 43% increased age-adjusted risk of TIA for mostly dynamic work (driven by those who reported OPA that slightly raises heart rate), but this association was substantially attenuated in fully-adjusted model 4.

Table 2.4 shows incident stroke and TIA diagnoses by the proportion of cumulative years of exposure to mostly dynamic work with associated hazard ratios and 95% confidence intervals

derived from fully-adjusted Cox regression models. For stroke, risk increased monotonically from 0 to 75% and peaked among women who were exposed 50-75% of their work years (HR=1.69; 95% CI=1.12-2.55), exposure above 75% did not further increase risk. For TIA, risk was highest among women exposed 25-50% of their work years (HR=1.82; 95% CI=1.19-2.76); however, those exposed less than 50% or more than 75% of their work years were also at a substantially increased risk (HR=1.62), but not women exposed 50-75% of their working years (HR=1.03).

Table 2.5 displays the number of incident stroke cases for each OPA level by baseline CVD status with fully-adjusted hazard ratios and 95% confidence intervals. Among women *without CVD* at baseline, increased risks were observed for those who reported sitting and standing equally, mostly standing, and mostly dynamic work at their current job, and for those who reported mostly standing and mostly dynamic work at their longest held job.

Among women *with CVD* at baseline, an increased risk of stroke was observed for those who reported sitting and standing equally or mostly dynamic work at both their current and longest held job.

Table 2.6 displays the number of diagnosed incident TIA cases for each OPA level by baseline CVD status with fully-adjusted hazard ratios and 95% confidence intervals. Among women *without CVD*, those who reported mostly standing or mostly dynamic work at their current job were at a substantially increased risk of TIA. Respective risk estimates based on the longest held job were much lower and those who reported sitting and standing equally displayed a decreased risk of TIA compared with those who reported mostly sitting. Among women *with CVD*, those who reported sitting and standing equally at their current job experienced a 2.4-fold increased risk of TIA. Mostly standing and mostly dynamic work at the current job were also

associated with increased risks compared with mostly sitting. For the longest held job, women with CVD who reported sitting and standing equally and mostly dynamic work were at an increased risk of TIA.

Analyses by CVD status at baseline were also performed *without* adjustment by potentially mediating hemodynamic factors (rate pressure product) and showed similar stroke and TIA risks (Supplementary Tables 2.2-2.3).

Table 2.7 shows the number of diagnosed incident stroke cases for each OPA level by baseline hypertension status with fully-adjusted hazard ratios and 95% confidence intervals. Risk patterns differed between those with and without hypertension. Among women *without hypertension*, mostly dynamic work was associated with an increased risk of stroke for both current and longest held job. Mostly standing or sitting and standing equally were associated with a decreased stroke risk for the longest held job. The lowest risk for stroke was observed for those mostly standing at their longest held job (HR=0.56; 95% CI=0.34-0.90); however, in models without adjustment for potentially mediating hemodynamic factors (Supplementary Table 2.4), mostly standing was not associated with any substantially reduced risk (HR=0.92; 95% CI=0.61-1.41) and, for current job, with an increased risk (HR=1.16; 95% CI=0.77-1.73).

Among women *with hypertension*, sitting and standing equally was associated with an increased risk of stroke at the current job, while mostly dynamic work was associated with a decreased risk. For the longest held job, all levels of OPA other than mostly sitting were associated with increased risks of stroke. Risks were similar in models without adjustment for potentially mediating hemodynamic factors (Supplementary Table 2.4).

Table 2.8 displays number of diagnosed incident TIA cases for each OPA level by baseline hypertension status with fully-adjusted hazard ratios and 95% confidence intervals. For

women *without hypertension* at baseline, an increased risk of TIA was observed for all OPA categories other than mostly sitting at the current job. In contrast, for the longest held job, sitting and standing equally and mostly standing were associated with reduced TIA risks, while mostly dynamic work was associated with an increased risk of TIA compared with mostly sitting.

Among women *with hypertension* at baseline, an increased risk of TIA was observed for all OPA categories other than mostly sitting at the current job with the highest risk for mostly dynamic work (HR=1.93; 95% CI=1.08-3.43). Mostly standing and mostly dynamic work at the longest held job were also associated with increased risks of TIA.

Results from models without adjustment for potentially mediating hemodynamic factors are presented in Supplementary Table 2.5 and indicate that adjustment for the rate pressure product reduced most effect estimates substantially.

Though this study was intended to examine the effects of OPA, we report the effects of WHO recommended levels of LTPA on stroke and TIA risk in Supplementary Table 2.6. If we consider these models to represent a preliminary assessment of the independent role of LTPA on cerebrovascular disease incidence, higher recommended levels of LTPA were inversely associated with both stroke and TIA risk. We estimated an inversely monotonic relationship between higher LTPA and stroke risk, with the strongest protective effect observed among those who participated in LTPA at >6 METs for 75+ minutes each week (HR=0.56; 95% CI=0.37, 0.85) compared with those who participated in no LTPA (the reference group). The relationship with TIA was less clear, though most levels of LTPA were protective of TIA risk.

2.5 Discussion

Summary of results. Overall, this comprehensive analysis found that OPA intensity and duration were generally positively associated with the risk of stroke and TIA among women. The

effect estimates, however, varied by the specific exposures and outcomes analyzed; monotonic positive dose-response relationships of OPA with TIA were found for current job, and with stroke for longest held job. In analyses of cumulative exposure, a smaller proportion of work years performing mostly dynamic OPA was associated with TIA risk, while a larger proportion was associated with stroke risk. Associations also differed by baseline CVD and hypertension status; stronger associations between OPA, stroke, and TIA were observed among women *without* these conditions than among women *with* these conditions at baseline.

Comparison of models with and without adjustment for hemodynamic factors indicated possible mediation of OPA effects by heart rate and blood pressure, especially for stroke risk among women *without* baseline hypertension; however, a formal mediation analysis was not performed in the absence of repeat measurements of heart rate and blood pressure. We accounted for recommended levels of LTPA in adjusted regression models and found that the highest levels of LTPA were inversely associated with both stroke and TIA risk.

The physical activity health paradox. Our results are consistent with the concept of the physical activity health paradox which, in brief, asserts that high LTPA is beneficial to cardiovascular health, while high OPA is detrimental.[208] Although high levels of OPA have historically been viewed as being beneficial to the cardiovascular system, recent evidence suggests that high OPA is an occupational health hazard;[53, 209, 210] the results of our study corroborate this notion for the first time with respect to cerebrovascular diseases. There are several hypotheses that explain the underlying mechanisms of this paradox; broadly, these can be grouped into two domains: biologic differences and structural differences between OPA and LTPA.[65]

Biologic differences include sustained inflammatory responses and prolonged elevation

of heart rate and blood pressure, all of which are associated with OPA but not with LTPA. Inflammation markers (e.g., C-reactive protein) have been shown to increase during all types of physical activity in the short-term, remaining elevated until the body has recovered.[229] High levels of OPA for prolonged periods during the work day—or over several days—without sufficient recovery time can result in sustained inflammation, one of the proposed mechanism in the development of atherosclerosis and other types of CVD.[51, 230, 231] Similarly, elevated resting and average 24-hour heart rate and blood pressure are known independent risk factors for CVD.[62-64, 232] High OPA over extended periods of time has been shown to increase 24-hour heart rate, an association not observed with shorter duration high levels of LTPA.[65] For instance, the Belgian Physical Fitness Study reported a more than 3-fold increased all-cause mortality risk among working men in the upper tertile of ambulatory 24-hour heart rate (HR=3.21; 95% CI=1.22-8.44).[66] Likewise, prolonged static OPA and heavy lifting have been shown to elevate blood pressure, even after working hours.[41] LTPA involving heavy lifting is common, but usually occurs for short periods of time and under controlled conditions, resulting in little impact on 24-hour blood pressure. In fact, short-term high intensity training can increase cardiorespiratory fitness, in turn lowering heart rate during rest and work; this reduces relative aerobic workloads (energy expenditure at work expressed as percent of cardiorespiratory fitness), which has been shown to be a stronger predictor of CVD than absolute measures of energy expenditure.[233, 234]

Structurally, the nature of OPA is different from LTPA, which may lead to poorer CVD outcomes through increased worker stress and fatigue. Participation in LTPA is voluntary and the participant is generally in complete control of their actions, including how much to do and when and how long to rest. Conversely, OPA is an employment requirement and usually

performed with little worker input: employees do not typically have control over work tasks, work hours, work speed, and other psychosocial, organizational, or ergonomic stressors that may be present in the work environment and determine the type, intensity, and duration of OPA. OPA is typically performed for longer time periods than LTPA and with less recovery time between and after activities. In addition to sustained inflammation as mentioned above, this can result in exhaustion and fatigue, which has been previously associated with an increase in CVD and stroke risk.[67-69]

The healthy worker survivor effect. It is important to acknowledge the possible impact of the so-called "healthy worker survivor effect" in analyses of occupational exposures and health. This concept can generally be described as a continuous selection process in which healthier workers remain in the workforce and unhealthier workers self-select out of the workforce. This phenomenon has previously been well-described and typically results in a conservative bias, i.e., attenuation of the effect of an occupational exposure.[235] For this reason, we expect the effect estimates in our study to underrepresent the true effect of OPA on stroke and TIA risk in women.

In our study, the healthy worker survivor effect is operating in two ways. First, our study was conducted in a population of women who were employed at baseline; we did not include women who had already left the workforce, perhaps for health reasons under study, which would again lead to a conservative bias. These women were excluded to assure consistency for the analyses of OPA exposure assessment based on current and longest held job (women not in the workforce at baseline would have only been considered in analyses of longest held job). This enabled us to compare the impact of using these alternative exposure assessment methods. Furthermore, including these women would have introduced misclassification of some self-reported covariates used for adjustment. For example, some health behaviors are dependent on

employment status,[236] especially among older adults;[237] because many covariates were only collected at baseline, we expected that adjusting for behaviors (e.g., LTPA) reported at times of unemployment when analyzing the impact of OPA at times of employment would bias our adjusted effect estimates in an unclear direction.

Second, our sensitivity analyses with stratification by baseline CVD status revealed different risk patterns that are also reflective of the healthy worker survivor effect. Individuals who developed CVD (and did not leave the workforce entirely because of their disease) may have transitioned from more demanding mostly dynamic work to more sitting work, resulting in an apparent higher risk of cerebrovascular disease the subgroup currently working jobs with lower levels of OPA. Results from Supplementary Table 2.7 support this notion: A larger percentage of individuals reported more dynamic levels of OPA for their longest held job but lower OPA for their current job, while a smaller percentage of women reported lower OPA at their longest held job and more dynamic OPA at their current job. These results were similar or stronger when restricted to women with CVD at baseline (results not shown), but nevertheless reflect the transition from high to low OPA in this population. At the same time, women without CVD at baseline are able to perform at higher OPA levels and constitute a highly selected group of the most resilient women with lower *a priori* risk for stroke and TIA, resulting in a downward conservative bias of cerebrovascular disease risks associated with high levels of OPA. Identification of the healthy worker survivor effect is important when interpreting the overall results of this study. We hypothesize the inclusion of all working women regardless of health status likely led to a conservative bias in our effect estimates. We therefore believe the true impact of dynamic OPA on stroke and TIA risk to be greater than estimated in this study.

The role of hemodynamic factors. Heart rate and blood pressure (combined as rate pressure product in our study) are hemodynamic cardiovascular risk factors that can be viewed both as mediators and confounders of the relationships between OPA and cerebrovascular disease; therefore, we chose to present results without (in models 3) and with adjustment for rate pressure product (in models 4). In most instances, adjustment for the rate pressure product did not substantially change effect estimates with the exception of analyses stratified by baseline hypertension status: Adjustment for the rate pressure product considerably changed the effects of OPA on cerebrovascular events among normotensive women (Supplementary Tables 2.4-2.5). There are competing explanations for these results. First, it is possible that hemodynamic factors are mediators in the relationship between OPA, stroke, and TIA; if so, the rate pressure product would be an intermediary on the causal path from exposure to outcome and controlling for it would introduce bias as a result of overadjustment.[238] Conversely, it may be that hemodynamic factors are not substantially determined by OPA but instead need to be considered potential confounders that need to be controlled; hence we provide results with and without adjustment for the rate pressure product.

In this study, women who reported cerebrovascular events had different hemodynamic characteristics than event-free women; however, these characteristics were also dependent on baseline hypertension status. Normotensive women who reported a stroke or TIA had, on average, higher values for all hemodynamic factors compared with normotensive women who did not report a cerebrovascular event (results not shown). Among hypertensive women, the opposite was true—hypertensive women who reported a cerebrovascular event had lower mean blood pressure than those who did not report a stroke or TIA. However, hypertensive women who reported cerebrovascular disease during follow-up were also more likely to report a

previous cardiovascular event at baseline; we hypothesize their lower mean blood pressure measurements were likely a product of better clinical blood pressure management post-event.

Strengths and limitations. Key strengths of this study include large sample size as well as detailed and complete information on occupational history and most relevant CVD risk factors including demographic, behavioral, work-related, and hemodynamic covariates. Potential bias from exposure misclassification was reduced by the availability and use of relatively detailed and specific OPA exposure measures. Most previous cohort studies broadly categorized OPA into 2-3 levels based on mostly arbitrary high/low cut-points,[21, 201, 203, 204] while our study employed a detailed, rank-order categorization with 4-6 levels of OPA describing specific combinations of work postures and dynamic work reflecting increasing physical demands. Though this exposure assessment tool has not been validated, it is an improvement from previous studies that relied on non-specific categorizations such as "high" and "low" OPA. Only one previous study used a validated questionnaire for exposure assessment[207] and its results were similar to ours insofar as it found increasing OPA to be positively associated with stroke risk.[206] Furthermore, in the Sister Study, OPA was assessed for each job held for at least 6 months since age 18, allowing for the creation and analysis of a cumulative OPA exposure measure in addition to measures based on current or longest held job. Using three different measures of OPA allowed us to assess whether or not there was a differential impact of more recent OPA (i.e., current job) and past OPA (i.e., longest held job and cumulative exposure to dynamic work) on the risk of stroke and TIA. Although there is substantial overlap in participant's reported OPA for current and longest held job (see Supplementary Table 2.7), differences exist (chi-square test p-value <0.0001) and may be responsible for the differential results regarding stroke and TIA. Conversely, these results could be a product of the healthy worker survivor effect—stroke may only be associated with

dynamic OPA at the longest held job because strokes often result in death or long-term disability. If women who experience a stroke are likely to drop out of the workforce or switch to lower OPA jobs, those who currently work jobs with dynamic OPA would consist of the healthiest and most resilient individuals, thus diluting the observed association between dynamic OPA at the current job and stroke.

Detailed information on important covariates allowed us to address confounding by considering a wide array of variables for adjustment and by employing incremental adjustment for potential confounders with sets of related variables. Additionally, adjusting for LTPA (as defined by WHO recommendation-based categories) allowed us to consider an important confounder that, to our knowledge, only one other study on the topic has taken into account. In addition, preliminary results on the independent LTPA effects from analytic models including both LTPA and OPA allowed us to determine if our results are compatible with the physical activity health paradox, which had not yet been examined for cerebrovascular diseases.

Our decision to analyze TIA as an outcome in addition to stroke is rarely seen in the epidemiologic literature on cerebrovascular disease. While stroke and TIA share many risk factors and are physiologically similar diseases,[199] they have potentially different impacts on functioning and quality of life. TIAs may represent an earlier stage of cerebrovascular disease than stroke and experiencing a TIA puts individuals at a high risk of stroke development in the future; in fact, it is estimated that 15% of all strokes are heralded by a TIA.[18] Additionally, TIAs confer a substantial short- and long-term risk of hospitalization for cardiovascular events and death in addition to stroke.[17] To our knowledge, this is the first study to report the impact of OPA on both stroke and TIA.

Our study was limited by the self-reported nature in which exposure and outcome were collected. Although next of kin were contacted in instances when the study participant died, very few of the cerebrovascular events in this study population were confirmed fatal by death records (n=8). We were unable to examine major stroke subtypes because this information was not collected as self-report was not expected to be reliable; however, nonfatal stroke cases are more likely to be ischemic than hemorrhagic and as such, we assume most reported stroke cases to be ischemic.[199] Although these subtypes share most risk factors, the extent to which these risk factors impact each subtype differs and thus our study would have been strengthened if we could have examined each subtype independently.[19, 199] While we were able to explore the role of potentially mediating hemodynamic factors by examining models with and without adjustment for the rate pressure product, our study would have benefited from repeated measures of heart rate and blood pressure in order to conduct mediation analyses that take into account changes over time. Furthermore, because stroke and TIA are relatively rare diseases, sample size limited the precision of some of our risk estimates. Yet, this is one of the largest studies to date that has explored the association between OPA and cerebrovascular disease in women. Furthermore, incidence rates of stroke in our study population are similar to those seen in comparable populations,[239] strengthening the generalizability of our results.

This study provides further support for the concept of the physical activity health paradox and suggests that increasingly dynamic OPA is a risk factor for both stroke and TIA for women in the workforce. Additional studies are needed to corroborate these findings and would benefit from more comprehensive exposure assessment with additional information on static workloads (carrying, lifting, holding tools, etc.) and work hour data, thus allowing for more precise assessment of cumulative exposure to OPA. Objective measures from accelerometers and heart

rate monitors would be desirable exposure assessment tools because they allow for the continuous measurement of relative aerobic workloads that take into account the cardiorespiratory fitness of the individual worker. Though it may not be feasible to implement these tools in a large cohort study, they could be used in smaller validation studies to assess the validity of self-reported exposure measures. Furthermore, this study would also benefit from using medical data that allowed for stratification by stroke subtype.

2.6 Tables

Table 2.1. Characteristics of the study population, stratified by cerebrovascular disease event status. Sister Study, 2004-2016, N=31270.[a]

Characteristic	No cerebrovascular event reported (N=30,703)		Cerebrovascular event reported[b] (N=567)	
Age	53.0	±7.6	57.7	±8.0
Race/ethnicity				
Non-Hispanic White	25295	82.4%	452	79.7%
Non-Hispanic Black	3146	10.3%	74	13.1%
Hispanic	1450	4.7%	24	4.2%
Other	802	2.6%	17	3.0%
Missing	10	0.0%	0	0.0%
Occupational physical activity, current job				
Mostly sitting	16808	54.7%	282	49.7%
Sitting and standing equally	6546	21.3%	132	23.3%
Mostly standing	4790	15.6%	97	17.1%
Continuous walking/movements[c]	2292	7.5%	50	8.8%
Heavy manual labor[d]	261	0.9%	6	1.1%
Sporadic heavy manual labor	6	0.0%	0	0.0%
Occupational physical activity, longest held job				
Mostly sitting	14895	48.5%	267	47.1%
Sitting and standing equally	6766	22.0%	115	20.3%
Mostly standing	5704	18.6%	106	18.7%
Continuous walking/movements[c]	2910	9.5%	73	12.9%
Heavy manual labor[d]	419	1.4%	6	1.1%
Sporadic heavy manual labor	4	0.0%	0	0.0%
Proportion of work years performing mostly dynamic work[e]				
0	22117	72.0%	374	66.0%
>0.00-<0.25	3875	12.6%	77	13.6%
0.25-<0.50	2276	7.4%	60	10.6%
0.50-<0.75	1314	4.3%	31	5.5%
≥0.75	1121	3.7%	25	4.4%
Leisure time physical activity				
None	5300	17.3%	130	22.9%
All activity <3 METs	18117	59.0%	321	56.6%
Insufficient activity time to meet requirements	1108	3.6%	28	4.9%
3-<6 METs for 150+ minutes/week	1527	5.0%	34	6.0%
6+ METs for 75+ minutes/week	4651	15.2%	54	9.5%
Alcohol consumption				

Never drinker	933	3.0%	29	5.1%
Former drinker	4124	13.4%	112	19.8%
<1-3 drinks/day	25414	82.8%	422	74.4%
>3 drinks/day	190	0.6%	1	0.2%
Missing	42	0.1%	3	0.5%
Smoking Status				
Never smoker	17820	58.0%	282	49.7%
Former smoker	10287	33.5%	221	40.0%
Current smoker	2583	8.4%	64	11.3%
Missing	13	0.0%	0	0.0%
Body mass index				
<18.5	315	1.0%	8	1.4%
18.5-24.9	11578	37.7%	148	26.1%
25.0-29.9	9576	31.2%	167	29.5%
30.0-34.9	5239	17.1%	147	25.9%
35.0-39.9	2456	8.0%	62	10.9%
≥40.0	1503	5.0%	35	6.2%
Missing	9	0.0%	0	0.0%
Ever face discrimination at work				
Yes	7077	23.1%	180	31.8%
No	20302	66.1%	321	56.6%
Missing	3324	10.8%	66	11.6%
Ever work night shifts				
Yes	9432	30.7%	195	34.4%
No	21271	69.3%	372	65.6%
Resting heart rate	69.0	±8.2	70.2	±8.5
Systolic blood pressure	114.0	±13.3	119.7	±14.9
Diastolic blood pressure	72.6	±8.8	74.5	±8.8
Pulse pressure	41.5	±9.1	45.2	±11.2
Rate pressure product[f]	2862.4	±730.8	3178.7	±930.5

[a]Data presented as number percentage% and mean ± standard deviation where appropriate.

[b]Defined by reported stroke or TIA during follow-up.

[c]Self-reported OPA as "continuous walking or other movements that increase your heart rate slightly"

[d]Self-reported OPA as "heavy manual labor that causes sweating or increases your heart substantially"

[e]Dynamic physical activity at work defined as self-reported OPA as "continuous walking or movements that raise your heart rate slightly," "heavy manual labor that causes sweating or increases your heart substantially," or "sporadic heavy manual labor."

[f]Rate pressure product defined as the product of pulse pressure and resting heart rate.

Table 2.2. Occupational physical activity and incident stroke risk (n=441): Hazard ratios and 95% confidence intervals from Cox regression analyses with incremental adjustment for potential confounders. Sister Study, 2004-2016, N=31270.

Occupational physical activity	Case N/ Exposed N	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Current job									
Mostly sitting	225/17090	1.00	-	1.00	-	1.00	-	1.00	-
Sitting and standing equally	105/6678	1.15	0.91-1.45	1.20	0.95-1.51	1.21	0.95-1.55	1.18	0.92-1.52
Mostly standing	70/4887	1.04	0.79-1.36	1.04	0.79-1.37	1.07	0.80-1.43	1.06	0.79-1.42
Mostly dynamic work	41/2615	1.25	0.89-1.74	1.13	0.81-1.58	1.07	0.74-1.54	1.02	0.70-1.49
Continuous walking/ movements	36/2342	1.22	0.86-1.73	1.12	0.79-1.60	1.04	0.70-1.53	0.98	0.66-1.47
Heavy manual labor	5/273	1.51	0.62-3.66	1.23	0.51-2.99	1.33	0.54-3.24	1.32	0.54-3.22
Longest held job									
Mostly sitting	198/15162	1.00	-	1.00	-	1.00	-	1.00	-
Sitting and standing equally	96/6881	1.00	0.78-1.28	1.02	0.80-1.31	1.02	0.79-1.33	1.02	0.79-1.33
Mostly standing	83/5810	1.07	0.82-1.38	1.03	0.80-1.34	1.08	0.82-1.42	1.07	0.81-1.41
Mostly dynamic work	64/3417	1.55	1.17-2.06	1.46	1.10-1.93	1.47	1.09-2.00	1.45	1.06-1.97
Continuous walking/ movements	59/2983	1.62	1.21-2.16	1.54	1.15-2.07	1.56	1.14-2.14	1.53	1.11-2.11
Heavy manual labor	5/434	1.03	0.43-2.51	0.86	0.35-2.09	0.94	0.39-2.30	0.94	0.38-2.29

[a]Model 1 adjusts for age

[b]Model 2 adjusts for age, leisure time physical activity, alcohol, smoking, and body mass index

[c]Model 3 adjusts for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, and night work

[d]Model 4 adjusts for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, night work, and rate pressure product

Table 2.3. Occupational physical activity and incident TIA risk (n=274): Hazard ratios and 95% confidence intervals from Cox regression analyses with incremental adjustment for potential confounders. Sister Study, 2004-2016, N=31270.

Occupational physical activity	Case N/ Exposed N	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Current job									
Mostly sitting	125/17090	1.00	-	1.00	-	1.00	-	1.00	-
Sitting and standing equally	66/6678	1.32	0.98-1.78	1.33	0.99-1.80	1.41	1.03-1.94	1.27	0.91-1.78
Mostly standing	51/4887	1.40	1.01-1.93	1.35	0.97-1.88	1.36	0.95-1.93	1.39	0.97-1.98
Mostly dynamic work	32/2615	1.75	1.19-2.58	1.57	1.06-2.32	1.83	1.22-2.74	1.63	1.07-2.48
Continuous walking/ movements	29/2342	1.77	1.18-2.65	1.58	1.05-2.38	1.85	1.21-2.81	1.66	1.07-2.57
Heavy manual labor	3/273	1.61	0.51-5.04	1.46	0.46-4.61	1.69	0.54-5.35	1.40	0.43-4.49
Longest held job									
Mostly sitting	130/15162	1.00	-	1.00	-	1.00	-	1.00	-
Sitting and standing equally	49/6881	0.80	0.57-1.11	0.82	0.59-1.14	0.87	0.62-1.22	0.88	0.62-1.25
Mostly standing	56/5810	1.11	0.81-1.51	1.02	0.74-1.40	1.09	0.78-1.53	0.91	0.63-1.30
Mostly dynamic work	39/3417	1.43	1.00-2.05	1.31	0.92-1.88	1.21	0.81-1.80	1.12	0.75-1.69
Continuous walking/ movements	37/2983	1.54	1.07-2.23	1.42	0.98-2.05	1.29	0.86-1.94	1.21	0.80-1.84
Heavy manual labor	2/434	0.62	0.15-2.50	0.55	0.14-2.23	0.64	0.16-2.58	0.54	0.13-2.21

[a]Model 1 adjusts for age

[b]Model 2 adjusts for age, leisure time physical activity, alcohol, smoking, and body mass index

[c]Model 3 adjusts for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, and night work

[d]Model 4 adjusts for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, night work, and rate pressure product

Table 2.4. Cumulative exposure to mostly dynamic occupational physical activity and incident stroke and TIA risk: Hazard ratios and 95% confidence intervals from fully-adjusted Cox regression analyses. Sister Study, 2004-2016, N=31270.

Cumulative occupational physical activity	Stroke (n=441)			TIA (n=274)		
	Case N/ Exposed N	HR[a]	95% CI	Case N/ Exposed N	HR[a]	95% CI
Proportion of work years performing mostly dynamic work[b]						
0	291/22200	1.00	-	175/22316	1.00	-
>0-<0.25	60/3892	1.15	0.85-1.57	40/3912	1.62	1.12-2.35
0.25-<0.50	45/2291	1.49	1.05-2.12	34/2302	1.82	1.19-2.76
0.50-<0.75	27/1318	1.69	1.12-2.55	11/1334	1.03	0.52-2.03
≥0.75	18/1128	1.35	0.80-2.28	14/1132	1.62	0.89-2.95

[a]Models adjust for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, night work, and rate pressure product

[b]Mostly dynamic work defined as self-reported occupational physical activity of "continuous walking or movements that raise your heart rate slightly," "heavy manual labor that causes sweating or increases your heart substantially," or "sporadic heavy manual labor."

Table 2.5. Occupational physical activity and incident stroke risk (n=441) by baseline cardiovascular disease (CVD): Hazard ratios and 95% confidence intervals from fully-adjusted Cox regression models. Sister Study, 2004-2016, N=31270.

Occupational physical activity	Cardiovascular disease status at baseline					
	Without CVD (n=25019)			With CVD[a] (n=6251)		
	Case N/ Exposed N	HR[b]	95% CI	Case N/ Exposed N	HR[b]	95% CI
Current job						
Mostly sitting	149/13514	1.00	-	76/3351	1.00	-
Sitting and standing equally	64/5292	1.11	0.82-1.50	41/1281	1.59	1.03-2.46
Mostly standing	51/3864	1.15	0.82-1.62	19/953	1.06	0.61-1.85
Mostly dynamic work	28/2057	1.21	0.78-1.88	13/517	1.25	0.64-2.46
Longest held job						
Mostly sitting	128/12059	1.00	-	70/2905	1.00	-
Sitting and standing equally	60/5411	1.01	0.73-1.40	36/1364	1.10	0.69-1.74
Mostly standing	57/4574	1.19	0.85-1.65	26/1153	0.98	0.58-1.64
Mostly dynamic work	47/2683	1.67	1.16-2.39	17/670	1.30	0.71-2.36

[a]Defined by self-reported doctor's diagnosis of congestive heart failure, mitral valve prolapse, arrhythmia, stroke, TIA, angina, or myocardial infarction at baseline.
[b]Models adjust for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, night work, and rate pressure product.

Table 2.6. Occupational physical activity and incident TIA risk (n=274) by cardiovascular disease (CVD): Hazard ratios and 95% confidence intervals from fully-adjusted Cox regression models. Sister Study, 2004-2016, N=31270.

Occupational physical activity	Cardiovascular disease status at baseline					
	Without CVD (n=25019)			With CVD[a] (n=6251)		
	Case N/ Exposed N	HR[b]	95% CI	Case N/ Exposed N	HR[b]	95% CI
Current job						
Mostly sitting	149/13514	1.00	-	76/3351	1.00	-
Sitting and standing equally	64/5292	1.09	0.74-1.62	41/1281	2.40	1.27-4.55
Mostly standing	51/3864	1.34	0.90-1.99	19/953	1.80	0.80-4.06
Mostly dynamic work	28/2057	1.70	1.06-2.72	13/517	1.24	0.45-3.45
Longest held job						
Mostly sitting	128/12059	1.00	-	70/2905	1.00	-
Sitting and standing equally	60/5411	0.69	0.45-1.06	36/1364	1.64	0.85-3.16
Mostly standing	57/4574	1.02	0.69-1.51	26/1153	1.03	0.46-2.30
Mostly dynamic work	47/2683	1.12	0.70-1.77	17/670	1.31	0.52-3.30

[a]CVD defined by self-reported doctor's diagnosis of congestive heart failure, mitral valve prolapse, arrhythmia, stroke, TIA, angina, or myocardial infarction at baseline.
[b]Models adjust for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, night work, and rate pressure product.

Table 2.7. Occupational physical activity and incident stroke risk (n=441) by baseline hypertension status: Hazard ratios and 95% confidence intervals from fully-adjusted Cox regression models. Sister Study, 2004-2016, N=31270.

Occupational physical activity	Hypertension status at baseline					
	Without hypertension (n=21893)			With hypertension[a] (n=9377)		
	Case N/ Exposed N	HR[b]	95% CI	Case N/ Exposed N	HR[b]	95% CI
Current job						
Mostly sitting	100/11792	1.00	-	125/5073	1.00	-
Sitting and standing equally	46/4597	0.98	0.67-1.43	59/1976	1.23	0.88-1.73
Mostly standing	38/3465	0.78	0.49-1.23	32/1352	1.04	0.68-1.59
Mostly dynamic work	27/1828	1.58	1.00-2.50	14/746	0.64	0.32-1.28
Longest held job						
Mostly sitting	96/10525	1.00	-	102/4439	1.00	-
Sitting and standing equally	40/4740	0.70	0.47-1.06	56/2045	1.21	0.84-1.73
Mostly standing	36/4044	0.56	0.34-0.90	47/1683	1.39	0.95-2.03
Mostly dynamic work	39/2373	1.71	1.15-2.55	25/980	1.15	0.70-1.89

[a]Defined by baseline systolic blood pressure ≥135, diastolic blood pressure ≥85, self-reported doctor's diagnosis of hypertension, or self-reported antihypertensive medication use.
[b]Models adjust for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, night work, and rate pressure product.

Table 2.8. Occupational physical activity and incident TIA risk (n=274) by baseline hypertension status: Hazard ratios and 95% confidence intervals from fully-adjusted Cox regression models. Sister Study, 2004-2016, N=31270.

Occupational physical activity	Hypertension status at baseline					
	Without hypertension (n=21893)			With hypertension[a] (n=9377)		
	Case N/ Exposed N	HR[b]	95% CI	Case N/ Exposed N	HR[b]	95% CI
Current job						
Mostly sitting	59/11833	1.00	-	66/5132	1.00	-
Sitting and standing equally	30/4613	1.18	0.73-1.90	36/1999	1.36	0.87-2.12
Mostly standing	33/3470	1.41	0.88-2.26	18/1366	1.08	0.62-1.88
Mostly dynamic work	16/1839	1.41	0.77-2.57	16/744	1.93	1.08-3.43
Longest held job						
Mostly sitting	67/10554	1.00	-	63/4478	1.00	-
Sitting and standing equally	22/4758	0.61	0.36-1.02	27/2074	0.93	0.58-1.51
Mostly standing	30/4050	0.82	0.50-1.33	26/1704	1.16	0.72-1.88
Mostly dynamic work	19/2393	1.16	0.67-2.02	20/985	1.27	0.71-2.28

[a]Defined by baseline systolic blood pressure ≥135, diastolic blood pressure ≥85, self-reported doctor's diagnosis of hypertension, or self-reported antihypertensive medication use.
[b]Models adjust for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, night work, and rate pressure product.

Supplementary Table 2.1. Characteristics of the study population, stratified by baseline cardiovascular disease (CVD) status. Sister Study, 2004-2016, N=31270.[a]

Characteristic	Without CVD (N=25019)		With CVD[b] (N=6251)	
Age	52.7	±7.6	54.5	±7.6
Race/ethnicity				
Non-Hispanic White	20581	82.3%	5166	82.6%
Non-Hispanic Black	2541	10.2%	679	10.9%
Hispanic	1212	4.8%	262	4.2%
Other	676	2.7%	143	2.3%
Missing	9	0.0%	1	0.0%
Occupational physical activity, current job				
Mostly sitting	13663	54.6%	3472	54.8%
Sitting and standing equally	5356	21.4%	1322	21.2%
Mostly standing	3915	15.7%	972	15.6%
Continuous walking/movements[c]	1862	7.4%	480	7.7%
Heavy manual labor[d]	218	0.9%	49	0.8%
Sporadic heavy manual labor	5	0.0%	1	0.0%
Occupational physical activity, longest held job				
Mostly sitting	12187	48.7%	2975	47.6%
Sitting and standing equally	5471	21.9%	1410	22.6%
Mostly standing	4631	18.5%	1179	18.9%
Continuous walking/movements[c]	2369	9.5%	614	9.8%
Heavy manual labor[d]	352	1.4%	73	1.2%
Sporadic heavy manual labor	4	0.0%	0	0.0%
Proportion of work years performing mostly dynamic work[e]				
0	18055	72.2%	4436	71.0%
>0-<0.25	3133	12.5%	819	13.1%
0.25-<0.50	1828	7.3%	508	8.1%
0.50-<0.75	1077	4.3%	268	4.3%
≥0.75	926	3.7%	220	3.5%
Leisure time physical activity				
None	4322	17.3%	1108	17.7%
All activity <3 METs	869	3.5%	267	4.3%
Insufficient activity time to meet requirements	14784	59.1%	3654	58.5%
3-<6 METs for 150+ minutes/week	1243	5.0%	318	5.1%
6+ METs for 75+ minutes/week	3801	15.2%	904	14.5%
Alcohol consumption				
Never drinker	755	3.0%	207	3.3%
Former drinker	3327	13.3%	909	14.5%

<1-3 drinks/day	20749	82.9%	5087	81.4%
>3 drinks/day	154	0.6%	37	0.6%
Missing	34	0.1%	11	0.2%
Smoking Status				
Never smoker	14543	58.1%	3559	56.9%
Former smoker	8319	33.3%	2189	35.0%
Current smoker	2146	8.6%	501	8.0%
Missing	11	0.1%	2	0.0%
Body mass index				
<18.5	235	0.9%	88	1.4%
18.5-24.9	9359	37.4%	2367	37.9%
25.0-29.9	7802	31.2%	1941	31.1%
30.0-34.9	4342	17.4%	1044	16.7%
35.0-39.9	2019	8.1%	499	8.0%
≥40.0	1253	5.0%	312	5.0%
Missing	9	0.0%	0	0.0%
Ever face discrimination at work				
Yes	5596	22.4%	1661	26.6%
No	16670	66.6%	3953	63.2%
Missing	2753	11.0%	637	10.2%
Ever work night shifts				
Yes	7545	30.2%	2082	33.3%
No	17474	69.8%	4169	66.7%
Resting heart rate	69.1	±8.2	68.6	±8.2
Systolic blood pressure	113.9	±13.2	114.9	±13.4
Diastolic blood pressure	72.6	±8.8	72.6	±8.8
Pulse pressure	41.3	±9.1	42.3	±9.5
Rate pressure product[f]	2858.1	±731.2	2908.1	±754.1

[a]Data presented as number percentage% and mean ± standard deviation where appropriate.

[b]CVD defined as self-reported doctor's diagnosis of congestive heart failure, mitral valve prolapse, arrhythmia, stroke, TIA, angina, or myocardial infarction at baseline.

[c]Self-reported OPA as "continuous walking or other movements that increase your heart rate slightly"

[d]Self-reported OPA as "heavy manual labor that causes sweating or increases your heart substantially"

[e]Dynamic physical activity at work defined as self-reported OPA of "continuous walking or movements that raise your heart rate slightly," "heavy manual labor that causes sweating or increases your heart substantially," or "sporadic heavy manual labor."

[f]Rate pressure product defined as the product of pulse pressure and resting heart rate.

Supplementary Table 2.2. Occupational physical activity and incident stroke risk (n=441) by pre-existing cardiovascular disease (CVD) status: Hazard ratios and 95% confidence intervals from Cox regression models adjusted for all potential confounders except rate pressure product. Sister Study, 2004-2016, N=31270.

Occupational physical activity	Cardiovascular disease status at baseline					
	Without CVD (n=25019)			With CVD[a] (n=6251)		
	Case N/ Exposed N	HR[b]	95% CI	Case N/ Exposed N	HR[b]	95% CI
Current job						
Mostly sitting	149/13514	1.00	-	76/3351	1.00	-
Sitting and standing equally	64/5292	1.12	0.82-1.51	41/1281	1.66	1.08-2.54
Mostly standing	51/3864	1.17	0.83-1.64	19/953	1.05	0.60-1.83
Mostly dynamic work	28/2057	1.25	0.81-1.92	13/517	1.25	0.64-2.46
Longest held job						
Mostly sitting	128/12059	1.00	-	70/2905	1.00	-
Sitting and standing equally	60/5411	0.99	0.72-1.37	36/1364	1.13	0.72-1.78
Mostly standing	57/4574	1.19	0.86-1.65	26/1153	0.96	0.57-1.62
Mostly dynamic work	47/2683	1.68	1.18-2.40	17/670	1.28	0.70-2.33

[a]CVD defined by self-reported doctor's diagnosis of congestive heart failure, mitral valve prolapse, arrhythmia, stroke, TIA, angina, or myocardial infarction at baseline.
[b]Models adjust for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, and night work.

Supplementary Table 2.3. Occupational physical activity and incident TIA risk (n=274) by pre-existing cardiovascular disease (CVD) status: Hazard ratios and 95% confidence intervals from Cox regression models adjusted for all potential confounders except rate pressure product. Sister Study, 2004-2016, N=31270.

Occupational physical activity	Cardiovascular disease status at baseline					
	Without CVD (n=25019)			With CVD[a] (n=6251)		
	Case N/ Exposed N	HR[b]	95% CI	Case N/ Exposed N	HR[b]	95% CI
Current job						
Mostly sitting	149/13514	1.00	-	76/3351	1.00	-
Sitting and standing equally	64/5292	1.11	0.76-1.64	41/1281	2.34	1.25-4.36
Mostly standing	51/3864	1.33	0.90-1.98	19/953	1.71	0.77-3.79
Mostly dynamic work	28/2057	1.74	1.10-2.77	13/517	1.11	0.41-3.03
Longest held job						
Mostly sitting	128/12059	1.00	-	70/2905	1.00	-
Sitting and standing equally	60/5411	0.69	0.45-1.05	36/1364	1.53	0.80-2.91
Mostly standing	57/4574	1.04	0.71-1.53	26/1153	1.02	0.46-2.27
Mostly dynamic work	47/2683	1.17	0.75-1.85	17/670	1.28	0.52-3.14

[a]CVD defined by self-reported doctor's diagnosis of congestive heart failure, mitral valve prolapse, arrhythmia, stroke, TIA, angina, or myocardial infarction at baseline.
[b]Models adjust for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, and night work.

Supplementary Table 2.4. Occupational physical activity and incident stroke risk (n=441) by baseline hypertension status: Hazard ratios and 95% confidence intervals from Cox regression models adjusted for all potential confounders except rate pressure product. Sister Study, 2004-2016, N=31270.

Occupational physical activity	Hypertension status at baseline					
	Without hypertension (n=21893)			With hypertension[a] (n=9377)		
	Case N/ Exposed N	HR[b]	95% CI	Case N/ Exposed N	HR[b]	95% CI
Current job						
Mostly sitting	100/11792	1.00	-	125/5073	1.00	-
Sitting and standing equally	46/4597	1.16	0.81-1.68	59/1976	1.24	0.89-1.73
Mostly standing	38/3465	1.16	0.77-1.73	32/1352	1.06	0.69-1.61
Mostly dynamic work	27/1828	1.57	1.00-2.47	14/746	0.71	0.37-1.36
Longest held job						
Mostly sitting	96/10525	1.00	-	102/4439	1.00	-
Sitting and standing equally	40/4740	0.88	0.59-1.30	56/2045	1.20	0.84-1.72
Mostly standing	36/4044	0.92	0.61-1.41	47/1683	1.34	0.92-1.95
Mostly dynamic work	39/2373	1.83	1.23-2.73	25/980	1.19	0.73-1.94

[a]Hypertension defined by baseline systolic blood pressure ≥135, diastolic blood pressure ≥85, self-reported doctor's diagnosis of hypertension, or self-reported antihypertensive medication use.
[b]Models adjust for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, and night work.

Supplementary Table 2.5. Occupational physical activity and incident TIA risk (n=274) by baseline hypertension status: Hazard ratios and 95% confidence intervals from Cox regression models adjusted for all potential confounders except rate pressure product. Sister Study, 2004-2016, N=31270.

Occupational physical activity	Hypertension status at baseline					
	Without hypertension (n=21893)			With hypertension[a] (n=9377)		
	Case N/ Exposed N	HR[b]	95% CI	Case N/ Exposed N	HR[b]	95% CI
Current job						
Mostly sitting	59/11833	1.00	-	66/5132	1.00	-
Sitting and standing equally	30/4613	1.26	0.79-2.00	36/1999	1.38	0.89-2.14
Mostly standing	33/3470	1.55	0.97-2.48	18/1366	1.06	0.61-1.84
Mostly dynamic work	16/1839	1.54	0.85-2.78	16/744	2.01	1.14-3.53
Longest held job						
Mostly sitting	67/10554	1.00	-	63/4478	1.00	-
Sitting and standing equally	22/4758	0.72	0.43-1.19	27/2074	0.96	0.60-1.54
Mostly standing	30/4050	0.99	0.62-1.59	26/1704	1.13	0.70-1.83
Mostly dynamic work	19/2393	1.19	0.68-2.06	20/985	1.35	0.76-2.38

[a]Hypertension defined by baseline systolic blood pressure ≥135, diastolic blood pressure ≥85, self-reported doctor's diagnosis of hypertension, or self-reported antihypertensive medication use.
[b]Models adjust for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, and night work.

Supplementary Table 2.6. Leisure time physical activity (LTPA) and incident stroke and TIA risk: Hazard ratios and 95% confidence intervals from fully-adjusted Cox regression analyses. Sister Study, 2004-2016, N=31270.

Leisure time physical activity[b]	Stroke (n=441)			TIA (n=274)		
	Case N/ Exposed N	HR[a]	95% CI	Case N/ Exposed N	HR[a]	95% CI
No LTPA	106/5324	1.00	-	67/5363	1.00	-
All activity <3 METs	24/1112	0.91	0.56-1.48	13/1123	0.61	0.31-1.22
Insufficient activity to meet requirements	251/18187	0.79	0.61-1.01	147/18291	0.86	0.62-1.20
Meets requirement of 3-<6 METs at 150+ mins/week	20/1541	0.71	0.42-1.18	20/1541	1.04	0.59-1.86
Meets requirement of 6+ METs at 75+ minutes/week	40/4665	0.56	0.37-0.85	27/4678	0.60	0.35-1.02

[a]Models adjust for age, occupational physical activity (current job), alcohol, smoking, body mass index, discrimination at work, night work, and rate pressure product

[b]LTPA categorized according to WHO recommendation-based categories; those who met both requirements listed were classified in the latter category in order to reflect more dynamic LTPA

Supplementary Table 2.7. Cross-tabulation of participant responses to occupational physical activity for current and longest held jobs.

Occupational physical activity, longest held job	Occupational physical activity, current job				
	Mostly sitting	Sitting and standing equally	Mostly standing	Continuous walking/ movements	Heavy manual labor
Mostly sitting	13077	1053	698	294	40
Sitting and standing equally	1857	4302	448	244	39
Mostly standing	1319	835	3354	269	33
Continuous walking/movements	730	420	334	1468	31
Heavy manual labor	110	68	53	67	136

Supplementary Table 2.8. Prevalence of occupational industry among women who reported mostly dynamic work for current or longest held job.

Occupational industry	Current job		Longest held job	
	n	**(%)**	**n**	**(%)**
Agriculture	56	(2.1)	85	(2.5)
Construction	35	(1.3)	47	(1.4)
Manufacturing	79	(3.0)	164	(4.8)
Retail	340	(13.0)	377	(11.0)
Transportation	93	(3.6)	152	(4.4)
Finance	63	(2.4)	60	(1.8)
Education	382	(14.6)	407	(11.9)
Medical/Healthcare	775	(29.6)	996	(29.1)
Social work	95	(3.6)	125	(3.7)
Entertainment	218	(8.3)	430	(12.6)
Service-based	191	(7.3)	203	(5.9)
Administrative	71	(2.7)	95	(2.8)
Other	217	(8.3)	276	(8.1)
Total	2615		3417	

Chapter 3. Parental occupational exposure to livestock or animal dust and the risk for childhood cancer in offspring

3.1 Abstract

In this population-based case-control study of Danish children aged <17 years, we identified 4,474 childhood cancer cases diagnosed 1968-2015 and frequency matched them to cancer-free controls by birth year and sex (n=422,022). Using a job exposure matrix (JEM), we identified parental occupational exposure to livestock and animal dust. Multivariable conditional logistic regression was used to estimate associations with childhood cancer risk. We estimated an increased risk for all central nervous system tumors in the offspring of fathers occupationally exposed to livestock or animal dust from the index child's birth to cancer diagnosis (OR=1.27; 95% CI=1.00, 1.63). We also detected an increased risk for astrocytoma in the offspring of mothers exposed from conception to birth (OR=1.89; 95% CI=1.00, 3.57) and an increased risk for neuroblastoma in the offspring of mothers exposed from birth to diagnosis (OR=1.88; 95% CI=0.99, 3.56). We examined births 1989+ to assess a period when exposures were more intensive due to a policy change regulating farm size and estimated a decreased risk for acute lymphoblastic leukemia in the offspring of fathers exposed after birth (OR=0.56; 95% CI=0.32, 1.00). Our results suggest that parental occupational exposure to livestock or animal dust may be implicated in the etiology of some childhood cancers, which could be due to infection or inflammatory/immune responses *in utero* or after birth.

3.2 Introduction

Occupational exposure to livestock has been linked to outbreaks of zoonoses such as Q-fever and Methicillin-resistant Staphyloccussaureas (MRSA), especially among pig and cattle farmers in Europe.[188-190, 240] These and other livestock-associated infections may spread from

animals to humans through direct contact or through contact with animal dander, particles from decomposing waste,[241] and aerosols generated by animal activity.[242] These infections can also spread from human to human, particularly in the households of infected workers.[191] Exposure to animal dusts from animal particles like hair, dander, or droppings can contribute to the spread of infection and may contain additional inflammatory agents, such as particulate matter or endotoxin.[243, 244] While large studies of adult cancers have revealed both positive and negative associations between cancer risk and occupational livestock work or animal contact,[245-248] research on whether or how this affects cancer risk in offspring is sparse.

Most childhood cancer studies of livestock risk have assessed the two most common pediatric cancer types, brain tumors and leukemia. Most but not all epidemiologic studies of childhood central nervous system (CNS) tumors have found positive associations with parental or childhood exposure to animals.[249-254] Studies of childhood leukemia have largely found no association with parental or childhood exposure to animals;[252, 255-257] however, one case-control study reported a decreased risk of acute lymphoblastic leukemia (ALL) with early childhood exposure to certain farm animals (i.e., cows, sheep, and poultry),[93] while a recent ecologic study reported a positive association between childhood leukemia and increasing density of hog operations.[258] Likely due to their rarity, other types of childhood cancer have not been widely studied in relation to parental or childhood livestock exposures.[132, 134, 252, 259]

There are several hypothesized mechanisms by which parental or childhood animal exposure could affect the development of childhood cancer. Etiologic agents of interest include zoonotic viruses, microbes, and animal dusts. Particulate matter and endotoxin from animal origin[260-262] can lead to chronic systemic inflammation and result in increased oxidative stress.[263-265] Oxidative stress is intricately involved in the process of carcinogenesis[266] and has also been

shown to alter paternal DNA during spermatogenesis[174, 175] and affect childhood development *in utero* and after birth.[267] Similarly, maternal infections during pregnancy can also interfere with fetal development;[268] because the developing fetal brain is particularly vulnerable to infection,[269] this suggests a role for infections in the etiology of childhood brain tumors specifically. Studies have shown that viruses can cause brain tumors in animals.[109-112] However, evidence for an association with humans is less conclusive; one study has reported a positive association between prior *Toxoplasma gondii* infection and gliomas in adults,[113] while other viruses have been detected, albeit with varying frequencies, in a number of pediatric and adult CNS tumor subtypes.[115]

Exposure after birth (due to a buildup of animal dusts in the home or parent-to-child transmission of exposure residues) could lead to carcinogenesis through changes to immune responses,[243, 244] or by directly transforming cells via inserting oncogenes into the host genome.[265] Alternatively, Greaves's "delayed infection" hypothesis suggests a protective role of infection for leukemia, asserting that exposure to common infections during early childhood reduces cancer risk.[98, 270]

In this population-based case control study of Danish children, we utilized a job-exposure matrix (JEM) to assess parental occupations with exposure to livestock or animal dust in order to examine the role of these types of exposures in the etiology of a variety of childhood cancers.

3.3 Methods

This case-control study is based on a linked database of all childhood cancers in Denmark (<17 years old) diagnosed between 1968 and 2015. The database utilized four different Danish data sources: the Central Population Registry (data available 1968-2014),[271] the Cancer Registry (1968-2015),[272] the Supplementary Pension Fund (1964-2014),[273] and the Medical Birth Registry

(1973-2014).[274] Linkage of these data sources was conducted by using a unique personal identification number allocated to each individual living in Denmark by the Central Population Registry. Because this was a record-based study, informed consent was not required. Approval for this study was received from the Danish Data Protection Agency and the human subjects' protection board at the University of California, Los Angeles.

We identified childhood cancer cases from the Cancer Registry and grouped them according to the International Classification of Childhood Cancer (ICCC), Version 1 until 2003 and Version 3 thereafter. Histological subtypes of childhood cancer were identified using the International Classification of Diseases for Oncology (ICD-O), Version 1 until 2003 and Version 3 thereafter. Overall, 5,669 cases of childhood cancer were identified. Controls, who were free of cancer at the date of diagnosis of the corresponding case, were randomly selected from the Central Population Registry and individually matched to cases by birth year and sex. Cases and controls were excluded from analyses if they were born outside of Denmark (n=5), did not have any parental occupational history for the time periods of interest (n=32,972), or were a case (or corresponding control) of a cancer type with fewer than 5 exposed cases throughout all four exposure windows (n=131,983). Our final sample consisted of 4,474 childhood cancer cases and 422,022 controls.

The source of parental information varies by child's birth year; this has been described in detail previously.[152] We obtained information on maternal and gestational factors from the Medical Birth Registry. Date of conception was calculated using child's gestational age as listed in the Medical Births Registry. For children born 1968-1972, no gestational age variable was available, and those children were assigned the average gestational age in the Danish population (40 weeks). For children born 1973-1977, a categorical gestational age variable in week ranges

(i.e., 37-42 weeks) was reported by midwives; to create a continuous variable, we assigned each child the midpoint value of their gestational age category. Children born 1978-1996 had gestational age recorded in weeks, and those born after 1997 had a value recorded in days. After creating a uniform gestational age variable, missing values remained in 3.9% of children. To address this, we used multiple imputations to assign children a gestational age value, using birthweight, birth length, placental weight, child's sex, birth place, maternal smoking status, labor interventions or procedures, and presence of congenital malformations as predictors when available. To address any potential biases introduced by our gestational age assignments, we conducted a sensitivity analysis using only children who had a recorded gestational age variable. For births prior to 1997, all data was primarily reported by midwives; since 1997, variables were automatically populated from the National Patient Register, though some information continued to be reported by midwives, like smoking status.

We obtained occupational histories for the parents of cases and controls from the Supplementary Pension Fund, which is compulsory for all salaried employees in Denmark aged 18-66 years who work at least nine hours per week; in 1978, persons aged 16-17 were additionally included. Students, individuals who are self-employed, and those born before April 1st, 1897 are not covered by the Supplementary Pension Fund.[273] The Danish industry code used for exposure classification is a five-digit extended version of the United Nation's four-digit International Standard Industrial Classification of All Economic Activities codes.[275] Occupations with animal dust exposure were identified using the Danish version of the Nordic Occupational Cancer Study job-exposure matrix,[276] while occupations with livestock exposure were additionally identified by an expert on Danish occupational health (J.H.). In order to avoid potential competing exposures (e.g., pesticides), we only included occupational codes which

specified work with livestock but not crops. Parents were classified as exposed if they had ever worked a job identified by our JEM during the timeframes of interest (Table 3.1).

Multivariable conditional logistic regression was used to examine associations between parental occupational exposure to livestock or animal dust during different developmental periods (i.e., preconception, pregnancy, and childhood) and the risk of childhood cancer in offspring.

We considered potential confounders identified in previous studies,[250, 252, 254] including parental age. We adjusted for other covariates, including parity (0, 1, or ≥2) and maternal smoking status (ever vs. never, in a sensitivity analysis of births 1991+ when smoking data were available), but effect estimates did not change by more than 10% and therefore these covariates were not included in final models. Because hog slaughtering was the most common profession in the JEM for mothers and fathers, we conducted a sensitivity analysis to examine the impact of these jobs alone; however, sample size only allowed for an analysis of paternal occupational exposure. We additionally conducted analyses stratified by child's birthplace (urban vs. rural/small towns). In order to address the impact of more intense livestock farming exposures over time, we conducted an analysis limited to births 1989+ to reflect the changes in livestock farming after the passage of a 1989 law that allowed famers to increase the size of their landholdings to 125 hectares.[277]

All statistical analyses were conducted using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3.4 Results

Demographic and gestational characteristics were similar between cases and controls, though a larger percentage of case mothers were multiparous at the time of birth of the index

child compared with control mothers (Table 3.2). More detailed information on covariates in relation to specific cancer types in this population has been reported previously.[152] Parents were frequently employed in the same occupation throughout the entire study period. Pearson correlation analyses revealed occupational livestock or animal dust exposures to be moderately correlated across the exposure periods of interest (fathers: r^2=0.66; mothers: r^2=0.60).

Paternal employment during both exposure windows was associated with an increased risk for CNS tumors in offspring, although associations were stronger with exposure from child's birth to cancer diagnosis (Table 3.3). We also observed an increased risk for germ cell tumor and rhabdomyosarcoma in the offspring of fathers occupationally exposed after birth. These associations were similar in sensitivity analyses restricting to paternal employment in hog slaughtering (Supplementary Table 3.1). Stronger associations were estimated for CNS tumors related to exposures during the preconception period, and for germ cell tumor and rhabdomyosarcoma in relation to exposures after birth.

For births 1989+ (presumably a time period with higher exposure), we found that paternal risks associated with CNS tumors were attenuated (Supplementary Table 3.2). This analysis also suggested an increased risk of bone tumors and Wilms tumor in the offspring of fathers occupationally exposed during preconception, and a similarly increased risk for rhabdomyosarcoma in the offspring of fathers exposed from birth to diagnosis. Furthermore, we detected an inverse association for acute lymphoblastic leukemia (ALL) in the offspring of fathers exposed from birth to diagnosis for births 1989+ (OR=0.56; 95% CI=0.32, 1.00).

In sensitivity analyses stratified by child's birthplace (urban vs. rural/small towns), we observed an increased risk for CNS tumors in the offspring of fathers exposed from preconception to conception if they were born in urban areas but not rural areas (Supplementary

Table 3.3); however, paternal employment from child birth to diagnosis was associated with an increased risk for CNS tumors in offspring born in both urban and rural areas. We also observed an increased risk for Wilms tumor in the offspring of fathers exposed to livestock or animal dust from preconception to conception if they were born in rural areas/small towns.

With respect to maternal exposures, the risk for astrocytoma increased in the offspring of mothers occupationally exposed from conception to birth. For neuroblastoma, we estimated an increased risk in relation to maternal exposure from birth to diagnosis (Table 3.4). In sensitivity analysis restricted to births 1989+, the effect estimates for both astrocytoma and neuroblastoma strengthened (OR=2.95; 95% CI=1.37, 6.36 and OR=2.93; 95% CI=1.35, 6.35, respectively) (Supplementary Table 3.4). We observed a decreased risk for all CNS tumors in the offspring of mothers exposed after birth among births 1989+ (OR=0.40; 95% CI=0.18, 0.90).

For children born in rural areas or small towns, but not for the urban born, the risk for bone tumors increased with maternal exposure from conception to birth (Supplementary Table 3.5). For children born in rural areas/small towns, associations with both astrocytoma and neuroblastoma were attenuated with maternal exposure from conception to birth and birth to diagnosis, respectively.

3.5 Discussion

Earlier studies of parental livestock exposure have mostly examined maternal farm residence with data collection and exposure assessment relying mainly on questionnaires.[249-251, 254] This study is one of the few to utilize registry-based occupational information to examine the impact of animal exposure in the offspring of exposed parents.[252, 253, 257] Our results suggest that parental occupational exposure to livestock or animal dust may play a role in the etiology of childhood cancer, but the impact of these exposures largely differs by cancer type. For rarer

types of childhood cancers, such as neuroblastoma, rhabdomyosarcoma, germ cell tumor, bone tumors, and Wilms tumor, our findings suggest parental occupational exposure to livestock or animal dust as a risk factor. During the latter half of the study period (1989+), our findings suggest a decreased risk for ALL in offspring of fathers exposed after the index child's birth, which is consistent with studies that have implicated early exposure to infectious diseases as protective for ALL.[93, 270, 278, 279]

Our findings did not corroborate past studies that reported positive associations between maternal exposure to animals and all CNS tumors in offspring;[249-252] however, our negative findings for exposure after birth are similar to a case-control study which detected inverse associations between exposure to specific animals (i.e., sheep, goats, and birds) in the first three years of life and childhood brain tumors.[249] We observed this decreased risk only when examining births 1989+. Larger land holdings allow for larger herd sizes: the average swine herd size increased from 169 pigs per year and farm in 1982 to nearly 3,000 in 2012; while cattle numbers have more than halved over the same period (reflecting a trend towards specialization in swine production), the average herd size more than doubled from 53 to 127 per holding.[280] Studies have shown that increasing herd size is predictive of seropositivity of certain zoonoses within herds and that herd size is positively associated with an increased risk of persistent infection within herds.[281-283] Because of this, we expect there to be a greater risk of infection in exposed workers during the latter half of the study period, which may explain why we observed higher effect estimates (when sample size allowed) among births 1989+. This was also reflected in our findings for a specific subtype of CNS tumors, astrocytoma; we observed positive associations during pregnancy which became stronger when assessing births 1989+. Only one previous study of maternal animal exposure stratified by multiple subtypes, but it similarly found

an increased risk of astroglial tumors among mothers exposed to animals during pregnancy.[249] Our results are mixed as they reveal both positive and inverse associations between maternal exposure and the risk of CNS tumors and their subtypes in offspring; however, it is possible that farm animal-related exposure is only implicated in the development of certain subtypes, e.g. astrocytomas and other glial tumors.

We also estimated positive associations between paternal occupational exposure, particularly exposure after birth, and all CNS tumors in offspring; while this relationship was weakened when examining exposures 1989+, the number of exposed cases was more than halved therefore producing a more imprecise estimate. Our results are similar to a previous study that examined paternal occupation in Great Britain, which found an increased risk for all CNS tumors with exposure to animals.[253] Similarly, a record-based analysis of parental occupation around conception in Denmark revealed an increased risk for CNS tumors in the offspring of fathers who worked as butchers (OR=7.0); while some data overlaps with the present study, only cases born 1968-1984 were included in this older analysis.[284] Our results are inconsistent with respect to parental exposure after births and total CNS tumor risk in offspring, as positive associations were observed with paternal exposure, while inverse associations were detected with maternal exposure. It is unclear why this disparity occurred.

While large confidence intervals limited the interpretation of our childhood leukemia findings, our results are generally compatible with an inverse relationship between parental occupational exposure and leukemia risk in offspring, particularly for exposures after birth. For births 1989+, we detected an inverse relationship between paternal occupational exposure after the index child's birth and ALL in offspring. Our findings are compatible with Greaves's "delayed infection" hypothesis, which suggests that exposure to common infections in early life

is protective for childhood ALL,[98] particularly subtype c-ALL, though we could not examine this in the present analysis because subtype information is not available in Cancer Registry records. Nevertheless, our results support the protective role of infection in the etiology of childhood leukemia.

We also detected associations with some rare types of childhood cancer. Although the literature is sparse with respect to most of these cancer types, some studies have investigated the role of animal exposures in their etiology. For neuroblastoma, one occupational analysis found that case mothers were more likely to report exposure to animal fur or feather dust compared with control mothers,[285] while other studies have reported inconsistent associations between agriculture or farm work and neuroblastoma risk in offspring, with wide confidence intervals.[252, 286, 287] To our knowledge, no study has previously reported on occupational or non-occupational animal contact and childhood germ cell tumor risk; while some evidence suggests that histological subtypes of germ cell tumors have different risk factors,[76] the exposed cases in our study consisted of heterogenous histologic types. With respect to rhabdomyosarcoma, an Italian case-control study found paternal employment as a butcher (OR=14.2) and maternal employment as a farmer (OR=7.0) to be associated with an increased risk of child's development of soft tissue sarcomas, though these estimates were based on a small number of cases.[259] To the best of our knowledge this is the first study to report on these exposures in relation to Wilms tumor.

More studies have investigated the role of parental farming exposures in the etiology of childhood bone tumors, but these did not differentiate between livestock and crop work, making it difficult to discern the relevant exposure. In these reports, parental farming exposures were associated with an increased risk of both Ewing's sarcoma and osteosarcoma in offspring.[132-135] Our findings did not appear to be driven by a specific histologic subtype of bone tumor; of the

six cases born 1989+ with fathers exposed from preconception to conception, three were Ewing's sarcoma cases and three were osteosarcoma cases. Similarly, of the five cases with mothers exposed from conception to birth, only one was a Ewing's sarcoma case while two were osteosarcoma cases. Our findings add to the body of literature on parental farm exposures and bone tumors in offspring and suggest that animal exposure may be relevant to their etiology, though it is possible other farm-related exposures are also implicated in childhood bone tumor development.

Our study was not affected by recall bias or selective participation due to its record-based nature. Because it was registry-based, we were unable to determine whether or not the parent listed is the biological parent for some birth years, though we have no reason to believe this would vary by case status.[152] We also utilized a JEM that includes a variety of understudied occupations that were selected to indicate specific exposure livestock and animal dust, such as furriers, pig farmers, and veterinarians. Previous studies have relied on cruder types of exposure assessment, combining together all farming jobs or using farm residence to assess exposure;[249-251, 254] these approaches inherently include competing exposures, such as pesticides, that may contribute to cancer development in children.[288] While the occupations included in our JEM were selected so they are not likely to include any competing exposures such as pesticides, the possibility of residual confounding still exists. Our study was limited by the small number of childhood cases, which resulted in imprecise estimates and the inability to stratify by subtype in some instances.

Our findings suggest that parental occupational exposure to livestock or animal dust may be implicated in the etiology of childhood cancer, perhaps due to exposure to infections or other inflammatory responses related to farm animal contact during pregnancy of after birth. Further

epidemiologic and mechanistic research is needed to further elucidate the relationship between these exposures and childhood cancer, with an emphasis on identifying specific hazardous and etiologic agents.

3.6 Tables

Table 3.1. Prevalence of occupations selected for inclusion in the livestock/animal dust job-exposure matrix, stratified by parent, exposure period of interest, and case/control status.

	Paternal exposure window								Maternal exposure window							
	Preconception to conception				Birth to diagnosis				Conception to birth				Birth to diagnosis			
	Controls N=(342,545)		Cases N=(3,734)		Controls N=(379,168)		Cases N=(4,158)		Controls N=(309,686)		Cases N=(3,460)		Controls N=(356,105)		Cases N=(3,939)	
Occupation title	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
All occupations in job-exposure matrix	7976	2.33	102	2.73	14377	3.79	172	4.14	3928	1.27	45	1.30	8007	2.25	82	2.08
Stud-farms	41	0.01	1	0.03	83	0.02	1	0.02	9	0.00	-		37	0.01	1	0.03
Farming, livestock	1529	0.45	18	0.48	3035	0.80	40	0.96	386	0.12	3	0.09	1002	0.28	12	0.30
Hog slaughtering	3740	1.09	46	1.23	6716	1.77	79	1.90	1141	0.37	12	0.35	2228	0.63	19	0.48
Meat-product/canning plants	838	0.24	12	0.32	1752	0.46	23	0.55	391	0.13	2	0.06	938	0.26	6	0.15
Cattle slaughterhouses	221	0.06	2	0.05	511	0.13	6	0.14	21	0.01	-		57	0.02	-	
Gut-cleaning plants	283	0.08	4	0.11	503	0.13	3	0.07	209	0.07	2	0.06	349	0.10	6	0.15
Poultry slaughterhouses	348	0.10	5	0.13	929	0.25	10	0.24	562	0.18	7	0.20	1350	0.38	16	0.41
Other meat preparation	82	0.02	3	0.08	281	0.07	4	0.10	65	0.02	-		190	0.05	2	0.05
Furriers	32	0.01	1	0.03	60	0.02	3	0.07	79	0.03	4	0.12	137	0.04	4	0.10
Fur preparation, etc.	8	0.00	-		68	0.02	-		21	0.01	1	0.03	90	0.03	1	0.03
Meat products, poultry, game	459	0.13	4	0.11	1226	0.32	9	0.22	189	0.06	1	0.03	446	0.13	2	0.05
Butcher shops, delicatessens	376	0.11	6	0.16	684	0.18	12	0.29	655	0.21	10	0.29	1356	0.38	16	0.41
Veterinarians	156	0.05	3	0.08	272	0.07	2	0.05	242	0.08	4	0.12	416	0.12	4	0.10

Table 3.2. Demographic, gestational, and parental characteristics of population cases and controls.

Characteristic	Cases (N=4,474)		Controls (N=422,022)	
	N	%	N	%
Child's sex				
Male	2411	53.9	227086	53.8
Female	2063	46.1	194936	46.2
Child's birthplace				
Urban	1564	35.0	145295	34.4
Rural/Small towns	2910	65.0	276725	65.6
Missing	0		2	
Maternal age (years)				
≤ 26	1332	29.8	127938	30.3
26-30	1695	37.9	158618	37.6
31-35	1016	22.7	99256	23.5
≥ 36	431	9.6	36210	8.6
Paternal age (years)				
≤ 25	692	15.6	68805	16.4
26-30	1551	34.9	142719	34.0
31-35	1287	29.0	124356	29.6
≥ 36	915	20.6	84044	20.0
Missing	29		2098	
Family socioeconomic status				
High	413	12.6	41217	13.4
Medium-high	575	17.5	53464	17.4
Medium	612	18.6	56191	18.3
Medium-low	1123	34.2	103577	33.7
Low	562	17.2	53162	17.3
Missing	1189		114411	
Parity				
0	353	7.9	35347	8.4
1	1874	41.9	204703	48.5
2+	2247	50.2	181972	43.1
Data available for births 1991+				
Maternal smoking status				
Smoker	492	25.8	46303	25.1
Non-smoker	1413	74.2	137956	74.9
Missing	69		6320	

Table 3.3. Adjusted odds ratios for paternal occupational exposure to livestock or animal dust and the risk of childhood cancer in offspring, stratified by exposure window.

Cancer type	Paternal exposure window							
	Preconception to conception				Birth to diagnosis			
	N	**%**	**OR[a]**	**aOR[b] (95% CI)**	**N**	**%**	**OR[a]**	**aOR[b] (95% CI)**
Controls	7976	2.33			14377	3.79		
Leukemias	34	2.41	**1.06**	1.07 (0.76-1.51)	54	3.43	**0.91**	0.93 (0.71-1.22)
ALL	27	2.39	**1.06**	1.07 (0.73-1.57)	42	3.35	**0.89**	0.91 (0.67-1.24)
AML	6	3.03	**1.30**	1.31 (0.58-2.95)	9	3.98	**1.05**	1.06 (0.54-2.07)
CNS tumors	34	2.76	**1.20**	1.19 (0.84-1.67)	68	4.85	**1.28**	1.27 (1.00-1.63)
Astrocytoma	6	1.50	**0.64**	0.62 (0.28-1.40)	15	3.20	**0.82**	0.80 (0.48-1.34)
Medulloblastoma	2	1.20		-	6	3.28	**0.89**	0.86 (0.38-1.94)
Bone tumors	7	3.52	**1.48**	1.50 (0.70-3.20)	10	4.24	**1.08**	1.10 (0.58-2.08)
Germ cell tumor	1	0.72		-	9	6.21	**1.60**	1.64 (0.83-3.23)
Neuroblastoma	9	3.32	**1.40**	1.39 (0.72-2.72)	9	3.20	**0.86**	0.86 (0.44-1.67)
Retinoblastoma	5	3.94	**1.70**	1.71 (0.69-4.19)	7	5.11	**1.56**	1.55 (0.72-3.33)
Rhabdomyosarcoma	4	2.99		-	9	6.47	**1.71**	1.68 (0.85-3.32)
Wilms tumors	8	3.60	**1.58**	1.58 (0.78-3.21)	6	2.46	**0.64**	0.66 (0.29-1.48)

[a]Crude odds ratios.

[b]Odds ratios adjusted for paternal age (continuous).

Table 3.4. Adjusted odds ratios for maternal occupational exposure to livestock or animal dust and the risk of childhood cancer in offspring, stratified by exposure window.

Cancer type	Maternal exposure window							
	Conception to birth				Birth to diagnosis			
	N	**%**	**OR[a]**	**aOR[b] (95% CI)**	**N**	**%**	**OR[a]**	**aOR[b] (95% CI)**
Controls	3928	1.27			8007	2.25		
Leukemias	12	0.92	**0.72**	0.74 (0.42-1.30)	31	2.07	**0.93**	0.95 (0.66-1.36)
ALL	9	0.86	**0.67**	0.69 (0.36-1.33)	18	1.50	**0.67**	0.69 (0.43-1.09)
AML	2	1.04		-	8	3.64	**1.59**	1.69 (0.83-3.43)
CNS tumors	15	1.28	**1.00**	0.98 (0.59-1.64)	25	1.84	**0.81**	0.79 (0.53-1.18)
Astrocytoma	10	2.58	**1.99**	1.89 (1.00-3.57)	11	2.40	**1.04**	1.00 (0.55-1.83)
Medulloblastoma	2	1.33		-	1	0.57		-
Bone tumors	5	2.53	**2.01**	2.02 (0.83-4.92)	7	3.00	**1.31**	1.33 (0.62-2.82)
Germ cell tumor	2	1.65		-	4	2.92		-
Neuroblastoma	4	1.63		-	10	3.98	**1.86**	1.88 (0.99-3.56)
Retinoblastoma	4	3.64		-	3	2.70		-
Rhabdomyosarcoma	0	0.00		-	1	0.73		-
Wilms tumors	3	1.61		-	1	0.48		-

[a]Crude odds ratios.

[b]Odds ratios adjusted for maternal age (continuous).

Supplementary Table 3.1. Adjusted odds ratios for paternal employment in hog slaughtering and the risk of childhood cancer in offspring, stratified by exposure window.

Cancer type	Paternal exposure window							
	Preconception to conception				Birth to diagnosis			
	N	**%**	**OR[a]**	**95% CI**	**N**	**%**	**OR[a]**	**95% CI**
Controls	3740	1.09			6716	1.77		
Leukemias	11	0.78	**0.74**	0.41-1.35	21	1.34	**0.78**	0.51-1.21
ALL	10	0.88	**0.84**	0.45-1.57	18	1.43	**0.85**	0.53-1.35
AML	1	0.51		-	2	0.88		-
CNS tumors	19	1.54	**1.43**	0.91-2.26	31	2.21	**1.23**	0.86-1.76
Astrocytoma	4	1.00		-	8	1.71	**0.89**	0.44-1.80
Medulloblastoma	1	0.60		-	2	1.09		-
Bone tumors	2	1.01		-	6	2.54	**1.41**	0.63-3.18
Germ cell tumor	1	0.72		-	6	4.14	**2.23**	0.98-5.09
Neuroblastoma	4	1.48		-	5	1.78	**0.98**	0.40-2.38
Retinoblastoma	2	1.57		-	3	2.19		-
Rhabdomyosarcoma	3	2.24		-	5	3.60	**2.02**	0.82-4.97
Wilms tumors	4	1.80		-	2	0.82		-

[a]Odds ratios adjusted for paternal age (continuous).

Supplementary Table 3.2. Adjusted odds ratios for paternal occupational exposure to livestock or animal dust and the risk of childhood cancer in offspring among births 1989+, stratified by exposure window.

Cancer type	Paternal exposure window							
	Preconception to conception				Birth to diagnosis			
	N	**%**	**OR[a]**	**95% CI**	**N**	**%**	**OR[a]**	**95% CI**
Controls	4206	2.38			6939	3.58		
Leukemias	13	1.86	**0.82**	0.47-1.41	18	2.31	**0.68**	0.42-1.09
ALL	9	1.60	**0.71**	0.37-1.37	12	1.93	**0.56**	0.32-1.00
AML	3	2.97		-	4	3.51		-
CNS tumors	17	2.67	**1.10**	0.68-1.79	30	4.27	**1.14**	0.79-1.66
Astrocytoma	2	1.03		-	7	3.17	**0.81**	0.38-1.72
Medulloblastoma	1	1.33		-	3	3.70		-
Bone tumors	6	6.19	**2.85**	1.24-6.56	5	4.35	**1.14**	0.46-2.82
Germ cell tumor	0	0.00		-	4	5.88		-
Neuroblastoma	5	4.10	**1.62**	0.66-3.98	5	3.76	**1.17**	0.48-2.87
Retinoblastoma	3	4.69		-	2	2.90		-
Rhabdomyosarcoma	3	3.75		-	6	7.32	**2.24**	0.96-5.22
Wilms tumors	5	5.05	**2.25**	0.91-5.59	2	1.85		-

[a]Odds ratios adjusted for paternal age (continuous).

Supplementary Table 3.3. Adjusted odds ratios for paternal occupational exposure to livestock or animal dust and the risk of childhood cancer in offspring, stratified by place of birth and exposure window.

Cancer type	Paternal exposure window							
	Preconception to conception				Birth to diagnosis			
	N	**%**	**OR[a]**	**95% CI**	**N**	**%**	**OR[a]**	**95% CI**
Place of birth: urban areas								
Controls	998	0.88			2024	1.55		
Leukemias	3	0.64		-	9	1.69	**1.15**	0.59-2.24
ALL	2	0.77		-	7	1.60	**1.12**	0.52-2.37
AML	0	0.00		-	1	1.52		-
CNS tumors	7	1.63	**1.94**	0.91-4.15	13	2.56	**1.71**	0.98-2.99
Astrocytoma	2	1.45		-	2	1.21		-
Medulloblastoma	1	1.85		-	3	5.08		-
Bone tumors	1	1.59		-	1	1.33		-
Germ cell tumor	0	0.00		-	1	1.85		-
Neuroblastoma	0	0.00		-	0	0.00		-
Retinoblastoma	0	0.00		-	0	0.00		-
Rhabdomyosarcoma	1	1.85		-	2	3.57		-
Wilms tumors	0	0.00		-	1	1.23		-
Place of birth: rural areas/small towns								
Controls	6978	3.05			12353	4.97		
Leukemias	31	3.30	**1.12**	0.78-1.61	45	4.33	**0.90**	0.66-1.21
ALL	24	3.23	**1.11**	0.74-1.67	35	4.28	**0.90**	0.64-1.26
AML	6	4.26	**1.40**	0.62-3.18	8	5.00	**1.02**	0.50-2.08
CNS tumors	27	3.36	**1.09**	0.74-1.61	55	6.14	**1.23**	0.94-1.62
Astrocytoma	4	1.52		-	13	4.28	**0.85**	0.48-1.48
Medulloblastoma	1	0.89		-	3	2.42		-
Bone tumors	6	4.41	**1.43**	0.63-3.26	9	5.59	**1.10**	0.56-2.17
Germ cell tumor	1	1.09		-	8	8.79	**1.83**	0.88-3.82
Neuroblastoma	9	5.49	**1.71**	0.87-3.37	9	5.33	**1.09**	0.55-2.13
Retinoblastoma	5	5.75	**1.95**	0.78-4.84	7	7.78	**1.87**	0.86-4.08
Rhabdomyosarcoma	3	3.75		-	7	8.43	**1.71**	0.78-3.75
Wilms tumors	8	5.41	**1.92**	0.94-3.92	5	3.07	**0.64**	0.26-1.55

[a]Odds ratios adjusted for paternal age (continuous).

Supplementary Table 3.4. Adjusted odds ratios for maternal occupational exposure to livestock or animal dust and the risk of childhood cancer in offspring among births 1989+, stratified by exposure window.

Cancer type	Maternal exposure window							
	Conception to birth				Birth to diagnosis			
	N	**%**	**OR[a]**	**95% CI**	**N**	**%**	**OR[a]**	**95% CI**
Controls	1932	1.16			3779	2.02		
Leukemias	5	0.71	**0.63**	0.26-1.51	13	1.65	**0.86**	0.50-1.50
ALL	4	0.71		-	8	1.27	**0.67**	0.33-1.35
AML	1	0.90		-	4	3.36		-
CNS tumors	8	1.28	**1.04**	0.51-2.09	6	0.85	**0.40**	0.18-0.90
Astrocytoma	7	3.52	**2.95**	1.37-6.36	4	1.79		-
Medulloblastoma	0	0.00		-	0	0.00		-
Bone tumors	2	1.98		-	4	3.39		-
Germ cell tumor	1	1.67		-	3	4.41		-
Neuroblastoma	2	1.57		-	7	5.47	**2.93**	1.35-6.35
Retinoblastoma	2	3.13		-	2	3.03		-
Rhabdomyosarcoma	0	0.00		-	0	0.00		-
Wilms tumors	1	1.03		-	0	0.00		-

[a]Odds ratios adjusted for maternal age (continuous).

Supplementary Table 3.5. Adjusted odds ratios for maternal occupational exposure to livestock or animal dust and the risk of childhood cancer in offspring, stratified by place of birth and exposure window.

Cancer type	Maternal exposure window							
	Conception to birth				Birth to diagnosis			
	N	**%**	**OR[a]**	**95% CI**	**N**	**%**	**OR[a]**	**95% CI**
Place of birth: urban areas								
Controls	578	0.55			1226	1.01		
Leukemias	2	0.45		-	4	0.79		-
ALL	1	0.28		-	3	0.73		-
AML	1	1.64		-	0	0.00		-
CNS tumors	4	0.93		-	7	1.41	**1.39**	0.65-2.98
Astrocytoma	3	2.19		-	3	1.84		-
Medulloblastoma	1	1.96		-	1	1.72		-
Bone tumors	0	0.00		-	1	1.25		-
Germ cell tumor	0	0.00		-	0	0.00		-
Neuroblastoma	1	2.08		-	3	3.16		-
Retinoblastoma	3	8.33		-	2	5.41		-
Rhabdomyosarcoma	0	0.00		-	0	0.00		-
Wilms tumors	0	0.00		-	0	0.00		-
Place of birth: rural areas/small towns								
Controls	3350	1.64			6781	2.89		
Leukemias	10	1.16	**0.72**	0.39-1.35	27	2.71	**0.97**	0.66-1.43
ALL	8	1.16	**0.73**	0.36-1.47	15	1.89	**0.68**	0.41-1.13
AML	1	0.76		-	8	5.23	**1.84**	0.90-3.77
CNS tumors	11	1.48	**0.88**	0.48-1.59	18	2.08	**0.68**	0.43-1.09
Astrocytoma	7	2.80	**1.61**	0.75-3.43	8	2.71	**0.88**	0.43-1.78
Medulloblastoma	1	1.01		-	0	0.00		-
Bone tumors	5	3.76	**2.46**	1.00-6.07	6	3.92	**1.42**	0.62-3.23
Germ cell tumor	2	2.50		-	4	4.49		-
Neuroblastoma	2	1.34		-	7	4.49	**1.57**	0.73-3.39
Retinoblastoma	1	1.35		-	1	1.35		-
Rhabdomyosarcoma	0	0.00		-	1	1.23		-
Wilms tumors	3	2.44		-	1	0.73		-

[a]Odds ratios adjusted for maternal age (continuous).

Chapter 4. Parental occupation and childhood germ cell tumor risk in Denmark, 1968-2015

4.1 Abstract

Childhood germ cell tumors (GCTs) are a rare group of neoplasms with varying histologic characteristics and relatively unknown etiology. Utilizing a linked database of five nationwide Danish registries, we developed a population-based case-control study of all childhood GCT cases in Denmark (<17 years old) diagnosed 1968-2015 (n=164) and birth year-matched controls (n=15,513). We conducted conditional multivariable logistic regression to analyze the association between parental occupation and childhood GCT risk in offspring, stratifying by common histologic subtype (i.e., yolk sac tumor and teratoma) when possible. We assessed parental exposures to specific chemicals, social contact, and shiftwork by job-exposure matrices (JEMs) applied to the individual parental employment histories. We found an increased risk of GCTs in the offspring of mothers occupationally exposed to high/very high social contact from child's conception to birth, especially among yolk sac tumors (OR=3.50; 95% CI=1.65, 7.43); this association persisted when examining maternal occupational exposure from birth to diagnosis (OR=2.77; 95% CI=1.29, 5.57). We also observed an elevated risk of all GCTs in the offspring of mothers who worked in the textile, clothing, and leather industry from birth to diagnosis (OR=2.19; 95% CI=1.09, 4.40). Paternal employment in the agriculture, forestry, and fishing industry from child's birth to diagnosis was associated with an increased risk of teratomas in offspring (OR=2.73; 95% CI=1.14, 6.78). Our findings suggest that parental occupation around pregnancy and after birth may be implicated in the etiology of childhood GCTs, with results varying by histologic subtype.

4.2 Introduction

Childhood germ cell tumors (GCTs) are a rare group of heterogenous neoplasms with largely unknown etiology.[141] In Europe, the incidence rate of GCTs for children ages 0-14 is estimated to be 4.8 per million.[140] In children, the two most common GCT subtypes are yolk sac tumors and teratomas; these subtypes may have different risk factors,[76, 141] but few studies have stratified by histologic subtype.

Despite the rarity of epidemiologic studies on childhood GCTs, consistent positive associations have been observed between cancer incidence and Asian/Pacific Islander race, birth defects, and abnormal fetal growth,[76, 146] the latter of which suggest that prenatal exposures are consequential to childhood GCT development. While parental occupation has been examined as a risk factor in the etiology of several childhood cancers, few studies have specifically examined the role of parental occupation in the development of childhood GCTs. These reports have shown positive associations between parental occupational exposure to chemicals/solvents and plastic/resin fumes and childhood GCT risk in offspring;[154] however, results were mixed or null for other occupational exposures, such as exhaust fumes, and no studies stratified by histologic subtype.[154, 158] Occupational and non-occupational studies have not been able to link parental pesticide exposure and childhood GCT risk.[143, 155, 164]

Non-occupational studies of certain chemicals or chemical groups have shown conflicting results with respect to *in utero* or early life exposure and childhood GCT risk. Our group recently found that ambient exposure to dichloromethane (a solvent often used in paint removers and other chemical processes) during pregnancy and the first year of life was positively associated with childhood GCTs, particularly teratomas.[165] We also previously estimated a weak positive association between traffic-related air pollution in pregnancy and childhood GCT risk, mostly for

teratomas.[144] Similarly, a Spanish case-control study estimated an imprecise but positive effect for childhood GCTs and proximity to urban areas with traffic pollution.[166] However, other case-control studies were unable to corroborate these findings.[154, 155, 167]

In this relatively large, Danish population-based case-control study, we sought to examine associations between parental occupation and offspring's risk for childhood GCT. Furthermore, we separately assessed two common histologic subtypes (i.e., teratoma and yolk sac tumor) to better elucidate the role of parental occupation in the etiology of this rare childhood cancer.

4.3 Methods

This population-based case-control study utilizes a linked database comprised of five nationwide Danish registries: The Central Population Registry (data available 1968-2017),[271] the Danish Cancer Registry (1968-2015),[272] the Supplementary Pension Fund (1964-2014),[273] the Medical Birth Register (1973-2014),[274] and the National Patient Register (1977-2017).[289] Exact linkage of information between registries is possible due to the existence of a 10-digit unique personal identifier, including information on birth day and sex, which has been applied to all residents in Denmark since 1968.

Childhood GCT cases (<17 years old) were identified according to the International Classification of Childhood Cancer (ICCC), Version 1 until 2003 and Version 3 thereafter, with codes 101-105 (n=166). Histologic subtypes of GCTs were identified using the International Classification of Diseases for Oncology (ICD-O), Version 1 until 2003 and Version 3 thereafter: yolk sac tumors (ICD-O code 9071; n=47) and teratomas (ICD-O codes 9080-9084; n=61) were most common in our population, while 58 GCT cases were coded as neither a teratoma nor a yolk sac tumor (germinomas, n=23; embryonal carcinoma, n=12; other, n=23). Controls, all of

whom were free of cancer at the date of diagnosis of the corresponding case, were randomly selected from the Central Population Registry and individually matched to cases at a 1:100 ratio by year of birth and sex, and had had to be alive at the date of diagnosis of the corresponding case. All children had to be born in Denmark in order to be eligible for this study. Cases and controls were excluded if both parents had no records in the Supplementary Pension Fund for all time periods of interest (n=1,087 including 2 cases). Our analytic dataset consisted of 164 GCT cases and 15,513 controls. Because this was a record-based study, informed consent was not required. Approval for this study was received from the Danish Data Protection Agency and the human subjects' protection board at the University of California, Los Angeles.

The source of parental information varies by child's birth year and has been described in detail elsewhere.[152] We obtained information on maternal and pregnancy related factors, including pregnancy and eventual labor complications from the Medical Birth Registry. We calculated date of conception using the child's gestational age as listed in the Medical Birth Registry. From 1968-1972, no gestational age variable was collected; therefore, children born during this period were assigned the average gestational age in the Danish population (40 weeks or 280 days). For the period 1973-1977, we had access to a categorical gestational age variable imputed in weeks and collected by midwives. Children born between 1978-1996 also had gestational age recorded in weeks. To transform this into a continuous variable, we assigned each child the midpoint value of their gestational age category. Children born after 1997 had a gestational age value recorded in days. For the 3.9% of children who had missing gestational age, multiple imputation was performed using birthweight, birth length, placental weight, child's sex, birth place, maternal smoking status, labor interventions or procedures, and presence of congenital malformations as predictors when available. Information on maternal smoking status

was first collected in 1991 and we created a binary variable to indicate whether the mother had ever smoked during pregnancy. Prior to 1997, information in the Medical Birth Registry was primarily provided by midwives; after 1997, most variables were automatically populated from hospital databases, though some information (e.g., smoking status) continued to be reported by midwives.

The National Patient Registry, a population-based administrative registry that has collected data from all Danish hospital since 1977,[289] was used to collect information on diagnosis of cryptorchidism (undescended testicle), a relatively strong risk factor for GCT development in males.[147] The National Patient Registry classified diagnoses according to the International Classification of Disease (ICD), Version 8 until 1993, with ICD-10 used thereafter; cryptorchidism was identified using ICD-8 code 752.1X and ICD-10 codes 53.XX. Validation studies have reported that accuracy of information in the National Patient Registry varies by diagnoses, with generally high positive predictive values ranging from below 15% to 100%, though no specific information on validity of cryptorchidism was available.[289]

The Supplementary Pension Fund, established in 1964, was used to obtain employment histories for the parents of cases and controls. At its inception, the Supplementary Pension Fund was compulsory for all salaried employees in Denmark aged 18-66 working at least nine hours per week; in 1978, persons aged 16-17 were additionally included. Individuals who are self-employed, students, and those born prior to April 1st, 1897 are not covered by the Supplementary Pension Fund.[273] All jobs held from three months before pregnancy for fathers and from conception for mothers, and until diagnosis or corresponding dates for controls were used to categorize industries and sub-industries according to a Danish five-digit detailed version of the International Standard Industrial Classification of All Economic Activities (ISIC).[275]

We targeted two different exposure periods for both mothers and fathers. For fathers, we examined jobs held from three months preconception to birth and from birth to the index child's cancer diagnosis. For mothers, we examined jobs held from conception to birth and from birth to the index child's cancer diagnosis.

We also utilized previously constructed JEMs[276] to examine occupational exposure to chemicals/solvents previously associated with GCTs: benzene, dichloromethane, gasoline, and toluene.[144, 165] The Danish JEMs were based off Finnish JEMs created as a part of the Nordic Occupational Cancer Study; the Danish version of the JEMs was based on measurements in Denmark by J.H.[290] The JEMs include industry-specific exposure estimates over four time periods: 1945-1959, 1960-1974, 1975-1984, and 1985+. Utilizing these JEMs, we created a binary exposure variable to indicate whether or not a parent had been exposed during the exposure windows listed previously. We additionally conducted a sensitivity analysis for JEM analyses of gasoline and toluene by restricting exposure to years after 1974, when benzene was less commonly used, as these solvents tend to be highly correlated.

We also examined occupational social contact by employing a JEM that replicated previous work by Kinlen et. al. and was updated for the Danish population based on the advice of experts in Danish occupational health.[101] Briefly, occupations with "very high" social contact predominantly consisted of elementary school teachers, daycare workers, and physicians, while "high" social contact occupations consisted of other teachers, healthcare professionals, hotel workers, pilots, police, hairdressers, and workers in the transportation industry; due to sample size restrictions, these two categories were combined. Occupations with "low" social contact (i.e., agricultural jobs) were included with all other jobs ("medium" social contact) to comprise the reference group.

Upon noticing an increased risk of GCTs in the offspring of mothers employed in hospital and health care work, we speculated that it could be due to known carcinogens such as infection or shiftwork. Thus, in a supplementary analysis, we utilized a previously constructed JEM[276] to assess maternal shiftwork exposure from conception to birth only. Occupations with "high" and "medium" shiftwork exposure were grouped together, while occupations with "low" shiftwork exposure were combined with all other jobs to make up the reference group. Some occupational codes belonged to more than one shiftwork exposure category; if this was the case, individuals were assigned the highest exposure category.

We employed conditional logistic regression to examine the association between parental occupation and childhood GCT risk in offspring. After considering adjustment for confounders identified in previous studies,[143, 146, 154] we adjusted for place of birth (parish) obtained from the Central Population Register and classified as urban and rural/small towns, and parental age (continuous; maternal age for maternal exposures and paternal age for paternal exposures). We additionally adjusted for maternal smoking status (ever v. never) in a sensitivity analyses of births after 1990, when the variable was first available. We also conducted sensitivity analyses, restricting to older mothers (ages 30+) and stratifying by child's place of birth (urban v. rural/small towns) and by child's age at diagnosis (<9 v. 9-16). When sample size allowed, we conducted sensitivity analyses differentiating the two most common histologic subtypes of GCTs in our population: teratomas and yolk sac tumors. In all analyses, we report on occupational exposures in which there were at least five exposed cases in either exposure window for mothers and fathers respectively.

All statistical analyses were conducted using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

4.4 Results

In our population, girls were more likely to be diagnosed with a yolk sac tumor, while boys were more commonly diagnosed with teratoma (Table 4.1). As expected, a significantly higher percentage of case males had a diagnosis of cryptorchidism compared with control males.

Compared with control parents, the parents of GCT cases were more likely to be older (≥36 years old) at the index child's birth and less likely to be ≤25 years. Children with teratomas were more likely to be born in small towns or rural areas, while children with yolk sac tumors were more likely to be born in urban areas, compared with controls.

Among fathers who worked in professional, scientific, and technical activities from three months preconception to the index child's birth, we estimated an increased risk of GCTs in offspring; however, this association was weaker when examining fathers employed in this industry from birth to the index child's cancer diagnosis (Table 4.2). We found an increased risk in GCTs in the offspring of fathers who held jobs in human health and social work activities from the child's birth to cancer diagnosis. This association was particularly pronounced among fathers employed in the sub-industry hospital and practitioner work from birth to cancer diagnosis. There were no associations between paternal exposure to specific solvents or social contact (as derived from JEMs) and childhood GCT risk in offspring.

In subgroup analyses of histologic subtype, we estimated an increased risk of teratomas in the offspring of fathers employed in agriculture, forestry, and fishing from the child's birth to cancer diagnosis (Table 4.3). There were no clear associations between paternal employment and yolk sac tumor risk in offspring.

Risk of GCTs were increased in the offspring of mothers employed in education and human health and social work activities from the index child's conception to birth (Table 4.4).

Among industry subcategories, these associations were stronger among the children of mothers who were employed in hospital and practitioner work and welfare institutions. Most of these associations persisted when examining mothers employed from the child's birth to cancer diagnosis; however, the association with welfare institutions was substantially weaker and less precise. We observed an increased risk of GCTs in offspring among mothers employed in the textile, clothing, and leather industry from the child's birth to cancer diagnosis. For exposure to solvents and social contact via JEMs, we estimated an increased risk of GCT in the offspring of mothers who were exposed to high/very high social contact from conception to birth, but not from birth to diagnosis. We also saw an increased risk of GCTs in mothers exposed to high/medium shiftwork from conception to birth (OR=1.71; 95% CI=1.16, 2.50); this association was slightly more pronounced for yolk sac tumors (OR=2.18; 95% CI=1.10, 4.34) than teratomas (OR=1.71; 95% CI=0.92, 3.19).

We found a substantial increased risk of yolk sac tumors in the offspring of mothers employed in both education and human health and social work activities from the child's conception to birth and from birth to cancer diagnosis (Table 4.5). Similarly, risk in yolk sac tumors was increased in the offspring of mothers exposed to high/very high occupational social contact from conception to birth and from birth to diagnosis. Risks for teratomas were also elevated in the offspring of mothers employed in human health and social work activities from the child's conception to birth; this association was attenuated when examining maternal employment from child's birth to cancer diagnosis.

Sensitivity analyses adjusting for maternal smoking (births 1991+ only), restricting to mothers aged 30 and older, and stratification by child's age at diagnosis resulted in no substantial changes in effect estimates. Stratification by child's place of birth, however, suggested higher

effect estimates for maternal employment in human health and social work activities among children born in rural/small towns compared with those born in urban areas (OR=2.29; 95% CI=1.43, 3.67 vs. OR=1.05; 95% CI=0.52, 2.14 for employment from conception to birth and OR=2.70; 95% CI=1.77, 4.14 vs. OR=0.87; 95% CI=0.46, 1.62 for employment from birth to diagnosis).

4.5 Discussion

This is one of few studies that examine parental occupation and childhood GCT risk and, to our knowledge, the first to examine specific histologic subtypes. The results of our population-based case-control study suggest that parental employment around pregnancy may influence the risk of GCTs in offspring; additionally, our findings suggest that certain exposures may be particularly relevant to certain GCT histologic subtypes of (i.e., yolk sac tumor or teratoma).

Across exposure windows, we found a consistent increased risk of GCTs, particularly yolk sac tumors, in the offspring of mothers who worked in the education and healthcare industries. While it is difficult to discern specific risk factors in these broad trades, a subgroup analysis of the healthcare industry indicated that these associations were primarily driven by women employed in hospital/practitioner work and welfare institutions, where night shift work is common. Sample size did not allow for a subgroup analysis in the education sectors. These associations could potentially be related to infectious and immunologic causes or to shiftwork and radiation. To our knowledge, no studies have investigated the role parental shiftwork may play in the etiology of childhood GCTs with the exception of the present analysis, which uncovered a positive association between maternal exposure from conception to birth, especially among yolk sac tumors. While radiation has been implicated as a risk factor for certain childhood cancers like leukemia and central nervous system tumors,[75, 291, 292] evidence for an association

with childhood GCTs is less clear. Past studies of radiation exposure have grouped GCTs with other solid tumors, likely due to their rarity, yielding inconsistent findings.[255, 292, 293] Nevertheless, our sensitivity analysis stratified by place of birth indicated higher risks among children born in rural areas/small towns compared with those born in urban areas. This suggests that infectious and immunologic causes may play a role based on the population mixing hypothesis which, in short, asserts that people who live in areas with lower population densities (i.e., rural areas) are more susceptible to infectious agents introduced by "incomers" who migrate to the area.[100] Our JEM-driven analysis suggested a moderately positive association between high/very high maternal occupational social contact and all GCTs in the offspring of mothers employed from conception to birth, but not from birth to diagnosis. This suggests *in utero* exposures may be more relevant for GCT etiology than exposures after birth. For mothers with occupational information in both exposure windows, there was a moderately high correlation between employment in the healthcare industry during pregnancy and from the child's birth to diagnosis (r^2=0.71), making it difficult to distinguish impacts of exposure according to time period.

Associations between maternal employment in the education and healthcare industries and GCT risk in offspring were mostly driven by associations with yolk sac tumors, as were associations with occupational social contact. It may be that immunologic or infectious causes are more relevant to the etiology of yolk sac tumors than teratomas. One previous study found no relationship between infections in pregnancy and GCT risk in offspring, however, associations were not stratified by subtype.[154] To our knowledge, no other study has examined maternal exposure to infections around pregnancy and GCT risk in offspring. Infections may play a role in yolk sac tumor development though methylation of the *GATA-4* transcription factor. Laboratory

studies have shown that *GATA-4* is expressed in human GCT lines that exhibit yolk sac differentiation, indicating a possible underlying biological process for these pediatric tumors.[294, 295] Other studies have shown methylation of *GATA-4* to be associated with the development of gastric cancer and chronic gastritis; and this was closely correlated with Helicobacter pylori infection, suggesting an infectious basis for gastric cancer.[296, 297] Taken together, it is possible that *in utero* or postnatal infection plays a role in pediatric yolk sac tumor development.

We also observed an increased risk of GCTs in the offspring of mothers employed in the textile, clothing, and leather industry from child's birth to cancer diagnosis. The case numbers did not allow us to determine if this was driven by a specific histologic subtype. Textile workers are typically exposed to textile-related dusts, including endotoxin, with minimal exposure to solvents; however, such exposure is common in dyeing and printing operations.[218, 298] Occupational textile work has mostly been associated with an increased risk of bladder and lung cancer in adults, with dye and asbestos exposure respectively identified as the etiologic agents of interest.[299] Yet, a study of parental occupation at periconception reported a positive association between occupational exposure to textile dust and childhood cancer in offspring for a combined category of solid tumors with different histologic makeups (including GCTs).[255] Other studies have reported a positive association between parental occupational dust or solvent exposure and GCTs in offspring,[154, 155] but it is unclear if these parents were employed in the textile industry.

Our JEM-driven analyses of occupational exposure to specific solvents revealed an elevated point estimate for GCT development in the offspring of mothers exposed to dichloromethane (also known as methylene chloride) from conception to birth, albeit imprecise. Dichloromethane is a solvent used in aerosols, paint removers, adhesives, and many chemical/industrial processes; it was recently classified as a probable human carcinogen (Group

2A) by the International Agency for Research on Cancer (IARC).[300] Our point estimate was similar to a recent analysis of California children (<6 years old) that suggested a positive relationship between ambient dichloromethane exposure during pregnancy (OR=1.52; 95% CI=1.11, 2.08) and GCT risk, particularly among teratomas.[165] We did not have sufficient sample size to stratify by histologic subtype in our analysis; of the nine case mothers exposed from conception to birth, only two had a child diagnosed with teratoma. *In utero* exposure to dichloromethane may disrupt differentiation and migration of early primordial germ cells during neonatal development, leading to carcinogenesis.[165, 301]

We found few associations between paternal employment and GCT risk in offspring. A positive association with childhood GCT was observed in the offspring of fathers employed in professional, scientific, and technical activities from three months preconception to conception; however, this grouping is a compilation of various occupations, with five case fathers employed in data processing, three in legal services, accounting, bookkeeping, and three in engineering, land inspectors, and architects. This occupational group may be a proxy for higher SES, though there was little difference in SES between cases and controls in our study. We found a moderately positive association between GCT risk in offspring and paternal employment in the agriculture, forestry, and fishing industry from birth to diagnosis; analyses of histologic subgroups suggested this was primarily driven by teratomas. Of the six exposed cases, three had fathers were employed in crop farming, one in livestock farming, one in fur faming, and one in agriculture, suggesting that pesticide exposure may be relevant in the etiology of teratomas. Past studies of occupational pesticide exposure have found no relationship with GCT risk in offspring;[143, 154, 155] however, some of these studies relied on self-reported exposure data[154, 155] and only one stratified by histologic subtype.[143]

This population-based case control study is record-based in nature, thus recall bias and self-selection due to participation does not affect exposure assessment or generate selection bias; however, because we relied solely on objectively recorded employment histories, JEMs, nondifferential misclassification is likely and would most likely bias our effect estimates towards the null. Limitations include the use of a social contact JEM that has not been validated for the presumed exposures associated with the employment historries,[101] though studies have previously found employment in healthcare and education industries to be associated with high rates of infectious disease.[302, 303] While we were able to stratify by histologic subtype in most instances, we lacked the sample size to do so for all occupational exposures. Nevertheless, this epidemiologic study is among the largest to examine parental occupational risk factors for childhood GCT development in offspring and was strengthened by the use of objective records, including a reliable cancer registry that captured cases over an extended period of time, and based in a country with free access to health care for all residents.

Our findings suggest that parental occupation, especially in the education and healthcare industries, may play a role in the etiology of GCT in offspring, though the exact mechanism by which these occupations impact childhood cancer risk in offspring is unknown. Further research is needed to corroborated the risk factors we identified, especially studies that are able to distinguish between histologic subtypes of childhood GCT.

4.6 Tables

Table 4.1. Demographic characteristics of germ cell tumor cases and controls (1968-2015).

Characteristic	Controls (N=15,513)		Germ cell tumor cases (n=164)					
			All GCTs		Teratomas (n=61)		Yolk sac tumors (n=45)	
Child's sex								
Female	7,177	(46.3)	75	(45.7)	31	(50.8)	16	(35.6)
Male	8,336	(53.7)	89	(54.3)	30	(49.2)	29	(64.4)
Cryptorchidism[a]								
Yes	206	(3.6)	6	(9.8)	2	(10.5)	1	(4.3)
No	5,573	(96.4)	55	(90.2)	17	(89.5)	22	(95.7)
Missing	109		0		0		0	
Maternal age group								
≤25	4,790	(30.9)	45	(27.4)	17	(27.9)	13	(28.9)
26-30	5,834	(37.6)	64	(39.0)	24	(39.3)	19	(42.2)
31-35	3,629	(23.4)	35	(21.3)	12	(19.7)	7	(15.6)
≥36	1,260	(8.1)	20	(12.2)	8	(13.1)	6	(13.3)
Paternal age group								
≤25	2,569	(16.7)	18	(11.0)	5	(8.2)	5	(11.1)
26-30	5,339	(34.6)	60	(26.6)	20	(32.8)	17	(37.8)
31-35	4,590	(29.8)	49	(29.9)	21	(34.4)	12	(26.7)
≥36	2,920	(18.9)	37	(22.6)	15	(24.6)	11	(24.4)
Missing	95		0		0		0	
Place of birth								
Urban	5,300	(34.2)	58	(35.4)	17	(27.9)	21	(46.7)
Small town or rural	10,213	(65.8)	106	(64.6)	44	(72.1)	24	(53.3)
Family socioeconomic status								
High	1,519	(13.1)	15	(12.6)	7	(16.7)	3	(10.0)
Medium-high	2,008	(17.4)	21	(17.6)	7	(16.7)	7	(23.3)
Medium	2,019	(17.5)	21	(17.6)	8	(19.0)	3	(10.0)
Medium-low	3,960	(34.2)	40	(33.6)	13	(31.0)	11	(36.7)
Low	2,057	(17.8)	22	(18.5)	7	(16.7)	6	(20.0)
Missing	3,950		45		19		15	

[a]Information on cryptorchidism is reported only for males and is available for births 1977+.

Table 4.2. Odds ratios and 95% confidence intervals for the association between paternal occupational exposures and germ cell tumor risk in offspring, stratified by exposure window (1968-2015).

	Paternal exposure window					
	Three months preconception to birth			Birth to diagnosis		
Occupational exposure	Case N/ Control N	OR[a]	aOR[b] (95% CI)	Case N/ Control N	OR[a]	aOR[b] (95% CI)
Total	143/13396			145/13480		
Occupational industry						
Agriculture, forestry, fishing	3/470	-	-	10/724	1.36	1.44 (0.75, 2.79)
Manufacturing	39/3556	1.04	1.06 (0.73, 1.53)	51/4859	0.95	0.98 (0.69, 1.39)
Food and drink industry	9/691	1.25	1.28 (0.65, 2.53)	16/1122	1.37	1.43 (0.84, 2.44)
Iron, metal works, foundries	20/1878	0.99	1.01 (0.63, 1.62)	26/2769	0.83	0.85 (0.56, 1.32)
Water supply, sewerage, etc.	3/154	-	-	5/460	1.04	1.05 (0.42, 2.61)
Construction	15/1767	0.75	0.77 (0.45, 1.32)	24/2514	0.86	0.89 (0.57, 1.39)
Retail and wholesale trade	29/2189	1.29	1.31 (0.87, 1.97)	33/3285	0.92	0.93 (0.63, 1.38)
Transportation and storage	14/1122	1.21	1.22 (0.70, 2.12)	19/1766	1.01	1.03 (0.63, 1.68)
Accommodation and food service activities	2/291	-	-	7/519	1.25	1.25 (0.58, 2.70)
Information and communication	7/585	1.15	1.14 (0.53, 2.45)	7/805	0.78	0.77 (0.36, 1.65)
Financial and insurance activities	4/445	-	-	5/621	0.77	0.76 (0.31, 1.87)
Professional, scientific, and technical activities	11/581	1.88	1.85 (0.99, 3.46)	15/967	1.51	1.49 (0.86, 2.57)
Administrative and support service activities	2/368	-	-	5/868	0.51	0.51 (0.21, 1.26)
Public administration and defense	22/2175	0.95	0.94 (0.59, 1.48)	40/3364	1.16	1.15 (0.79, 1.67)
Education	6/353	1.58	1.51 (0.66, 3.48)	10/718	1.30	1.25 (0.65, 2.40)
Human health and social work activities	7/662	1.00	0.97 (0.45, 2.09)	20/1247	1.60	1.57 (0.97, 2.54)
Hospital and practitioner work	6/501	1.13	1.10 (0.48, 2.51)	18/970	1.85	1.82 (1.10, 3.02)
Other service activities	2/184	-	-	7/444	1.52	1.49 (0.69, 3.23)
Job exposure matrix						
Benzene	13/1385	0.84	0.85 (0.48, 1.51)	26/2199	1.09	1.11 (0.72, 1.72)
Dichloromethane	19/1962	0.89	0.90 (0.55, 1.46)	33/2989	1.02	1.04 (0.70, 1.54)
Gasoline	11/1253	0.79	0.80 (0.43, 1.48)	23/2013	1.05	1.07 (0.68, 1.69)
Birth years >1974[c]	10/1054	0.91	0.92 (0.48, 1.76)	18/1632	1.06	1.09 (0.65, 1.81)
Toluene	20/2101	0.85	0.87 (0.54, 1.39)	36/3259	1.02	1.04 (0.71, 1.53)
Birth years >1974[c]	18/1762	0.98	0.99 (0.60, 1.65)	31/2673	1.15	1.17 (0.77, 1.78)
High/very high social contact	11/925	1.14	1.10 (0.59, 2.04)	18/1658	1.04	1.02 (0.62, 1.68)

[a]Crude odds ratios.

[b]Odds ratios adjusted for birth place (urban v. small towns/rural) and paternal age (continuous).

[c]Restricted to years when benzene was less commonly used.

Table 4.3. Odds ratios and 95% confidence intervals for the association between paternal occupational exposures, yolk sac tumor, and teratoma risk in offspring, stratified by exposure window (1968-2015).

	Paternal exposure window					
	Three months preconception to birth			Birth to diagnosis		
Occupational exposure	Case N/ Control N	OR[a]	aOR[b] (95% CI)	Case N/ Control N	OR[a]	aOR[b] (95% CI)
Yolk sac tumors	39/13396			41/13480		
Occupational industry						
Manufacturing	9/3556	0.81	0.85 (0.40, 1.82)	12/4859	0.87	0.96 (0.48, 1.92)
Retail and wholesale trade	9/2189	1.57	1.58 (0.74, 3.36)	8/3285	1.03	1.06 (0.48, 2.32)
Public administration and defense	5/2175	0.78	0.75 (0.29, 1.94)	10/3364	1.31	1.26 (0.61, 2.60)
Job exposure matrix						
High/very high social contact	5/925	1.88	1.70 (0.66, 4.38)	6/1658	1.56	1.41 (0.58, 3.40)
Teratomas	52/13396			49/13480		
Occupational industry						
Agriculture, forestry, fishing	2/470	-	-	6/724	2.73	2.78 (1.14, 6.78)
Manufacturing	14/3556	1.07	1.07 (0.57, 1.99)	16/4859	0.83	0.84 (0.45, 1.55)
Food and drink industry	5/691	1.96	2.02 (0.79, 5.16)	6/1122	1.57	1.60 (0.66, 3.88)
Iron, metal works, foundries	7/1878	1.01	1.02 (0.46, 2.28)	7/2769	0.66	0.66 (0.30, 1.50)
Construction	10/1767	1.54	1.60 (0.79, 3.23)	11/2514	1.31	1.34 (0.67, 2.68)
Retail and wholesale trade	10/2189	1.20	1.24 (0.62, 2.50)	10/3285	0.79	0.81 (0.40, 1.64)
Transportation and storage	4/1122	-	-	6/1766	0.97	1.00 (0.42, 2.37)
Public administration and defense	9/2175	1.11	1.08 (0.52, 2.22)	15/3364	1.44	1.44 (0.77, 2.70)
Human health and social work activities	4/662	-	-	5/1247	1.17	1.14 (0.44, 2.93)

[a]Crude odds ratios.

[b]Odds ratios adjusted for birth place (urban v. small towns/rural) and paternal age (continuous).

Table 4.4. Odds ratios and 95% confidence intervals for the association between maternal occupational exposures and germ cell tumor risk in offspring, stratified by exposure window (1968-2015).

Occupational exposure	Maternal exposure window					
	Conception to birth			Birth to diagnosis		
	Case N/ Control N	OR[a]	aOR[b] (95% CI)	Case N/ Control N	OR[a]	aOR[b] (95% CI)
Total	121/11261			137/12510		
Occupational industry						
Manufacturing	16/1615	0.89	0.92 (0.54, 1.58)	29/2744	0.98	1.03 (0.67, 1.57)
Textile, clothing, and leather industry	1/277	-	-	9/434	2.07	2.19 (1.09, 4.40)
Iron, metal works, foundries	7/534	1.29	1.33 (0.62, 2.89)	16/1083	1.45	1.52 (0.89, 2.59)
Retail and wholesale trade	11/1371	0.73	0.77 (0.41, 1.44)	22/2310	0.87	0.90 (0.57, 1.44)
Transportation and storage	5/274	1.73	1.71 (0.69, 4.25)	5/490	0.96	0.96 (0.39, 2.36)
Accommodation and food service activities	1/258	-	-	5/661	0.70	0.77 (0.31, 1.89)
Information and communication	3/337	-	-	8/595	1.23	1.24 (0.60, 2.56)
Financial and insurance activities	8/446	1.73	1.69 (0.81, 3.50)	10/604	1.66	1.64 (0.85, 3.15)
Professional, scientific, and technical activities	2/341	-	-	5/607	0.78	0.78 (0.32, 1.92)
Administrative and support service activities	0/209	-	-	6/732	0.78	0.79 (0.34, 1.81)
Public administration and defense	40/3734	1.01	0.98 (0.66, 1.44)	66/6813	0.81	0.82 (0.58, 1.16)
Education	8/326	2.40	2.30 (1.10, 4.79)	13/862	1.46	1.42 (0.79, 2.55)
Human health and social work activities	38/2294	1.75	1.73 (1.17, 2.56)	58/3697	1.79	1.79 (1.27, 2.54)
Hospital and practitioner work	32/1818	1.86	1.82 (1.21, 2.75)	51/2892	2.00	1.99 (1.39, 2.83)
Daycares, kindergartens, and homes for children	1/189	-	-	5/433	1.12	1.13 (0.46, 2.80)
Welfare institutions	8/333	2.23	2.25 (1.08, 4.67)	12/844	1.37	1.39 (0.76, 2.55)
Other service activities	1/240	-	-	6/578	0.96	0.97 (0.42, 2.22)
Job exposure matrix						
Benzene	2/496	-	-	11/1131	0.91	0.96 (0.51, 1.80)
Dichloromethane	9/661	1.33	1.37 (0.69, 2.71)	12/1312	0.84	0.87 (0.48, 1.59)
Gasoline	2/449	-	-	11/1042	1.00	1.06 (0.56, 1.99)
Birth years >1974[c]	2/386	-	-	7/852	0.78	0.80 (0.37, 1.74)
Toluene	5/754	0.61	0.66 (0.26, 1.58)	15/1592	0.87	0.90 (0.52, 1.56)
Birth years >1974[c]	5/650	0.71	0.72 (0.29, 1.78)	10/1318	0.69	0.70 (0.36, 1.36)
High/very high social contact	14/946	1.45	1.43 (0.82, 2.49)	24/2042	1.16	1.15 (0.74, 1.80)

[a]Crude odds ratios.
[b]Odds ratios adjusted for birth place (urban v. small towns/rural) and maternal age (continuous).
[c]Restricted to years when benzene was less commonly used.

Table 4.5. Odds ratios and 95% confidence intervals for the association between maternal occupational exposures, yolk sac tumor, and teratoma risk in offspring, stratified by exposure window (1968-2015).

	Maternal exposure window					
	Conception to birth			Birth to diagnosis		
Occupational exposure	Case N/ Control N	OR[a]	aOR[b] (95% CI)	Case N/ Control N	OR[a]	aOR[b] (95% CI)
Yolk sac tumors	34/11261			38/12510		
Occupational industry						
Manufacturing	4/1615	0.78	0.85 (0.29, 2.48)	6/2744	0.87	0.89 (0.36, 2.18)
Public administration and defense	11/3734	0.96	1.03 (0.50, 2.13)	13/6813	0.67	0.69 (0.34, 1.39)
Education	5/326	5.07	4.59 (1.69, 12.45)	6/862	3.63	3.57 (1.42, 9.01)
Human health and social work activities	14/2294	2.85	2.73 (1.36, 5.48)	20/3697	3.52	3.48 (1.82, 6.68)
Hospital and practitioner work	11/1818	2.57	2.56 (1.23, 5.32)	17/2892	3.39	3.41 (1.77, 6.56)
Job exposure matrix						
High/very high social contact	9/946	3.77	3.50 (1.65, 7.43)	10/2042	2.85	2.77 (1.29, 5.57)
Teratomas	44/11261			46/12510		
Occupational industry						
Manufacturing	6/1615	0.94	0.93 (0.39, 2.25)	10/2744	1.03	1.07 (0.52, 2.21)
Retail and wholesale trade	3/1371	-	-	9/2310	1.12	1.17 (0.55, 2.48)
Public administration and defense	14/3734	0.98	0.92 (0.48, 1.76)	22/6813	0.88	0.88 (0.48, 1.61)
Human health and social work activities	15/2294	2.06	2.15 (1.14, 4.06)	16/3697	1.33	1.35 (0.72, 2.52)
Hospital and practitioner work	12/1818	2.00	2.02 (1.03, 3.98)	14/2892	1.48	1.49 (0.78, 2.83)
Job exposure matrix						
High/very high social contact	3/946	-	-	5/2042	0.71	0.72 (0.28, 1.85)

[a]Crude odds ratios.

[b]Odds ratios adjusted for birth place (urban v. small towns/rural) and maternal age (continuous).

Chapter 5. Public health relevance

In this dissertation, we report on cerebrovascular disease and childhood cancer as they relate to occupational exposures in vulnerable populations. It is important to note the public health relevance of our findings, particularly the burdens associated with these rare diseases and the steps that can be taken to prevent them.

There are substantial economic and social costs associated with cerebrovascular disease. In the United States, the average third-party and out-of-pocket costs accompanying an ischemic stroke hospitalization from 2006-2015 ranged from $24,448 for patients discharged without a disability to $73,903 for patients discharged with disability. In the first year after discharge, total mean costs for patients without a disability were $30,132, while the cost for patients with a disability were $46,850.[304] In addition to increasing economic burden, strokes reduce quality of life and limit everyday functioning. A study of stroke patients in Luxembourg found that two years post-event, 44.7% of patients reported impaired sensory function, 35.1% had impaired motor function, and 31.9% reported impaired memory function.[305] As the average lifespan of the population continues to increase, stroke incidence—and the associated economic and social costs—are expected to increase as well, further highlighting the need for prevention of cerebrovascular disease.

While our findings regarding OPA and cerebrovascular disease are relatively novel, our results have the potential to impact real-world policies given corroboration from additional studies. In our analysis, women who reported mostly dynamic work were most commonly employed in the healthcare, entertainment, education, or retail industries (see Supplementary Table 2.8). Because jobs in these industries often involve prolonged standing, long hours, and—with respect to the healthcare and retail industries—varying work schedules, they are perhaps the

most effective industries to target worksite interventions aimed at reducing high levels of OPA. Potential policies of interest include increasing the frequency and duration of breaks at work and reducing work hours; however, worker input is strongly encouraged when designing any worksite intervention, given they are made aware of the hazards of their job.

Childhood cancers are inherently associated with high costs because they are diagnosed early in life and require serious medical treatment. Although the burden of treatment varies by cancer type, a study of 1,651 pediatric and adolescent cancer patients in Utah found that, 10 years after diagnosis, patients with cancer incurred an average of $51,723 more in charges, spent more time in the hospital, and were more frequently admitted to the hospital compared with children without cancer.[306] In fact, this study estimated that children diagnosed with cancer in 2014 would incur over $800 million more in hospital charges by 2024 compared with cancer-free children. While advances in medicine have made it easier to treat childhood cancer and reduce mortality rates, there has been little progress with respect to not only prevention of childhood cancer, but identifying etiologic agents associated with this rare disease.

Our studies of parental occupational exposures and childhood cancer in offspring less clearly lend themselves to real-world policy changes. However, our findings add to a growing body of literature on the etiology of childhood cancer, where many studies face similar limitations—namely, small sample size and the difficulty utilizing a prospective study design. Nevertheless, our findings are important, should be considered in light of these limitations, and will hopefully encourage more research in this relatively understudied field.

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