Dog Ownership and Cardiovascular Disease

MWENYA MUBANGA
Dissertation presented at Uppsala University to be publicly examined in Humanistiska Teatern, Engelska parken, Thunbergsvägen 3, Uppsala, Tuesday, 9 October 2018 at 09:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English. Faculty examiner: Professor Unnur Valdimarsdottir (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12A, 171 77 Stockholm and Faculty of Medicine at the University of Iceland).

Abstract

The relationship between pet ownership and human health has been studied extensively; however, the effect of dog ownership on human health has had conflicting results. The overall aim of this research project was to investigate the impact of dog ownership, and the death of the dog, on human cardiovascular health and all-cause mortality.

Study I was a population-based study investigating the association between dog ownership with the risk of cardiovascular disease (CVD) and death. Of 3,432,153 individuals included, dog ownership (13.1%) was associated with a lower risk of CVD- and all-cause death by 23% and 20%, respectively. In single-person households, there was an inverse association between dog ownership and incident CVD, as well as a stronger inverse association with CVD-death and all-cause death.

Study II was a population-based study investigating the association between dog ownership and initiation of treatment for cardiovascular risk factors in 2,026,865 adults. Dog ownership (14.6%) was associated with a slightly elevated risk of initiating treatment (2%) for hypertension and dyslipidaemia, but not for diabetes mellitus. However, some evidence for residual confounding was found.

Study III investigated the risk of death after hospitalization for a first-ever acute myocardial infarction (n=181,696) or first-ever ischemic stroke (n=157,617) in two population-based cohorts. Dog ownership was associated with a 20% to 24% lower risk of all-cause mortality and CVD-death, respectively.

In Study I-III, ownership of hunting breed dogs was associated with the lowest risk of the outcomes, while owning dogs of mixed pedigree was associated with worse cardiovascular health.

Study IV found evidence of an increased risk of CVD after the loss of a life-insured pet (dog or cat; n=147,251) during the first week, 3-6 months after and 6-12 months after pet-loss.

This thesis has used the Swedish population and health registers to investigate the relationship between various aspects of dog ownership and cardiovascular risk. By using defined, quantifiable end-points and robust statistical methods, this project has made an important contribution to the body of research underlying the positive relationship between dog ownership and cardiovascular health, paving the way for further research into causal mechanisms.

Keywords: dog ownership, cardiovascular risk, cardiovascular disease, pet ownership

Mwenya Mubanga, Department of Medical Sciences, Molecular epidemiology, Husargatan 3, Biomedicinskt Centrum (BMC), Uppsala University, SE-75123 Uppsala, Sweden.

© Mwenya Mubanga 2018

ISSN 1651-6206
urn:nbn:se:uu:diva-357629 (http://urn.kb.se/resolve?urn:nbn:se:uu:diva-357629)
To my precious family....your love has always been the wind beneath my sails
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


II. Mwenya Mubanga, Liisa Byberg, Agneta Egenvall, Johan Sundström, Patrik K Magnusson, Erik Ingelsson, Tove Fall. Dog Ownership and Cardiovascular Risk Factors: a nationwide prospective register-based cohort study *(Submitted manuscript)*

III. Mwenya Mubanga, Liisa Byberg, Agneta Egenvall, Erik Ingelsson, Tove Fall. Dog ownership and mortality after a major cardiovascular event – a register-based prospective study *(Submitted manuscript)*

IV. Mwenya Mubanga*, Daniela Mariosa*, Agneta Egenvall, Fang Fang, Erik Ingelsson, Liisa Byberg, Tove Fall. The impact of death of a pet on major acute cardiovascular risk in the owner: a register-based cohort study *(Manuscript)*

*Authors contributed equally to this work

Reprints were made with permission from the respective publishers.
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>11</td>
</tr>
<tr>
<td>Definition of CVD</td>
<td>11</td>
</tr>
<tr>
<td>Human-animal companionship</td>
<td>12</td>
</tr>
<tr>
<td>Dog ownership and cardiovascular risk factors</td>
<td>13</td>
</tr>
<tr>
<td>Dog ownership and physical activity</td>
<td>13</td>
</tr>
<tr>
<td>Dog ownership and hypertension</td>
<td>14</td>
</tr>
<tr>
<td>Dog ownership and dyslipidemia</td>
<td>14</td>
</tr>
<tr>
<td>Dog ownership, obesity and diabetes mellitus</td>
<td>15</td>
</tr>
<tr>
<td>Dog ownership and psychosocial factors</td>
<td>15</td>
</tr>
<tr>
<td>Dog ownership and cardiovascular disease and death</td>
<td>17</td>
</tr>
<tr>
<td>Cardiovascular health in Sweden</td>
<td>18</td>
</tr>
<tr>
<td>Dog ownership in Sweden</td>
<td>19</td>
</tr>
<tr>
<td>Rationale for Current Work</td>
<td>20</td>
</tr>
<tr>
<td>Project objectives</td>
<td>20</td>
</tr>
<tr>
<td>Specific aims</td>
<td>20</td>
</tr>
<tr>
<td>Materials and Methods</td>
<td>22</td>
</tr>
<tr>
<td>The Swedish Population and Health Registers</td>
<td>23</td>
</tr>
<tr>
<td>Register of the Total Population</td>
<td>23</td>
</tr>
<tr>
<td>The Longitudinal Integration Database for Health Insurance and Labor Market Studies</td>
<td>23</td>
</tr>
<tr>
<td>The Swedish National Patient Register</td>
<td>23</td>
</tr>
<tr>
<td>The Swedish Prescribed Drug Register</td>
<td>24</td>
</tr>
<tr>
<td>The Cause of Death Register</td>
<td>24</td>
</tr>
<tr>
<td>The Swedish Twin Registry</td>
<td>24</td>
</tr>
<tr>
<td>The Screening Across the Lifespan Twin (SALT) study</td>
<td>24</td>
</tr>
<tr>
<td>TwinGene</td>
<td>25</td>
</tr>
<tr>
<td>The Pet Registers</td>
<td>25</td>
</tr>
<tr>
<td>The Swedish Kennel Club</td>
<td>25</td>
</tr>
<tr>
<td>The Swedish Board of Agriculture Dog Register</td>
<td>25</td>
</tr>
<tr>
<td>The Agria Pet Insurance Registry</td>
<td>26</td>
</tr>
<tr>
<td>Ethical approval</td>
<td>26</td>
</tr>
<tr>
<td>Data security</td>
<td>26</td>
</tr>
<tr>
<td>Main exposures, outcomes and confounders</td>
<td>27</td>
</tr>
<tr>
<td>Exposures</td>
<td>27</td>
</tr>
</tbody>
</table>
Abbreviations

ATC  Anatomical Therapeutic Chemical Classification System
AHA  American Heart Association
BMI  Body Mass Index
CI   Confidence interval
CVD  Cardiovascular disease
HR   Hazard Ratio
ICD  International Classification of Diseases
MACE Major Acute Cardiovascular Event
NHANES National Health and Nutritional Examination Study
PIN  Personal Identity Number
RTP  Register of the Total Population
SALT Screening Across the Lifespan Twin study
Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally.\(^1\) Despite increased primary prevention, there were an estimated 422.7 million prevalent cases of CVD in 2015.\(^2\) In Europe alone, CVD accounted for more than 4 million (45%) of all deaths,\(^3\) with the vast majority of deaths attributed to ischemic heart disease and stroke.\(^1,3\) Although disability-adjusted life years (DALY) due to CVD have been falling in most European countries over the last fifteen years, CVD presently accounts for the loss of more than 64 million DALYs in Europe (23% of all DALYs), thus presenting significant costs in terms of hospital and out-patient care.\(^4\)

Cardiovascular diseases generally have a complex etiology, with both genetic and environmental factors contributing to disease development. Whilst certain CVD risk factors, including age, sex, ethnicity and genetic susceptibility, are non-modifiable; the two large international INTERHEART (n=29,972)\(^5\) and INTERSTROKE (n=26,919)\(^6\) studies estimated that about 90% of all acute myocardial infarction and stroke events could be attributed to potentially modifiable risk factors, listing hypertension, dyslipidaemia, diabetes mellitus, psychosocial factors, tobacco use, abdominal obesity, physical inactivity, suboptimal nutrition and alcohol use.\(^5,6\) The combined effect of the different modifiable risk factors exponentially increases the risk of CVD, however, each factor is independently important.\(^6\)

Significant advances in the primary and secondary prevention of CVD have resulted in lower mortality rates globally;\(^7\) however, novel approaches are needed to decrease the impact of each of the modifiable risk factors. This thesis investigates the potential role of dog ownership in cardiovascular morbidity and mortality.

Definition of CVD

Cardiovascular disease encompasses a class of disorders affecting the heart and peripheral blood vessels. The diseases may affect the coronary arteries, the heart itself, the hearts’ conduction system and also the peripheral blood vessels, including the central nervous system arteries.

Atherosclerosis is one of the most commonly occurring forms of biologically-mediated vascular injury leading to stenosis or occlusion.\(^8\) It is the result
of multiple complex mechanisms, many of which remain unclear. Atherosclerotic CVD includes two main conditions: ischemic heart disease and cerebrovascular disease (mainly ischemic stroke). In the present thesis, we focused on the diagnoses acute myocardial infarction (International Classification of Disease (ICD-10 I21), heart failure (ICD-10 I50, ischemic stroke (ICD-10 I63) and hemorrhagic stroke (ICD-10 I60-I62). These diagnoses constitute the vast majority of deaths due to CVD.

Human-animal companionship

“Native peoples say that a long time ago on the earth a chasm opened up separating animals and humans. As the chasm got wider and wider, the dogs jumped across to be with the humans. Today, when you hear wolves howling in the night, they’re crying out for the chasm to close” - (Kling, 2006)

Humans and dogs share a long intertwined history. Although the time, location and nature of the first domestication is unclear, it is believed that dogs were initially kept for security, hunting and pulling loads, but the relationship between man and dog has evolved over time to establish a mutually beneficial co-existence more recently associated with psychological, physiological and social benefits, particularly for the owner.

During the past three decades, there has been an increase in research on the benefits of pet ownership (both dogs and cats) and human–animal interaction. Some studies have found that adult pet owners live longer and have fewer health problems than non-pet owners. Others have also shown positive psychological effects of pet ownership: pet owners tend to be less lonely, less depressed, and more socially engaged, and more likely to perceive their communities as more cohesive than non-pet owners. Interactions with pets are also thought to reduce stress, with a number of studies reporting decreases in blood pressure and/or increases in heart rate variability following interactions with pets. Interactions with dogs have been shown to reduce cortisol levels suggesting that the benefits of interactions with pets may be mediated, in part, through hypothalamic-pituitary-adrenal (HPA) axis activity. Similarly, interactions with dogs increase levels of oxytocin, a neuropeptide expressed in many areas of the brain and related to attachment and social affiliative behavior.

Research shows that the choice to get a pet and the type of pet may have important correlates with the owner’s personality, age, socio-economic status and ethnicity. Dog owners have been described as outgoing, more likely to enjoy physical activity and to exhibit more positive health-related characteristics than non-pet owners. In the elderly, the need for companionship and regular physical activity are the most common reasons for choosing to own either a cat or dog. Whilst these are popularly held perceptions about
Dog owners, the studies used to characterize them have largely been conducted in people aged ≥65, 32-34 living in rural areas, 35,36 or in homogenous populations.29,31

In an American survey (n=42,044), dog ownership was associated with a married status, older age, higher household income and living in a more rural location.33 Similarly, a Brazilian study (n=13,555) showed that dog ownership was more common in persons of older age and in households with higher income.36 In contrast, a survey in Australia (n=5,079) reported that pet owners, including dog owners, tended to have lower levels of education and lower paying jobs37 indicating that the association with a high socioeconomic status is not consistent internationally.33,36,38 In addition, although studies find that families with children in the home are more likely to have dogs,33,39 a strong emotional bond (pet attachment) is assumed to be highest amongst those living alone or childless couples and the newly married.40,41 Research that characterizes the initial motivation for acquiring a dog is needed.

According to Mullersdorf et al, pet ownership in Sweden specifically, is most common in individuals aged 35-49; house owners; those who enjoy physical and outdoor activities, and those who work part-time.28 This postal survey (n=39,995) was limited by its restriction to the central parts of Sweden and a 36.0% non-response rate.28 It is possible that those in full time employment were least likely to respond. In 2012, a telephone-based survey by Statistics Sweden found that the most commonly owned companion animals in the country were dogs and cats - approximately 13% of all households owned a dog and 17% owned a cat.42

Dog ownership and cardiovascular risk factors

Dog ownership and physical activity

Regular physical activity is an established protective factor for the prevention and treatment of leading non-communicable diseases, including cardiovascular disease and diabetes.7 According to the World Health Organization, 23% of adults in high income countries are insufficiently physically active, and these levels continue to rise.43 The benefits of dog ownership on physical activity levels are widely reported.44,45 Dog owners are generally shown to achieve more than the recommended amount of physical activity than non-owners,46,47 and reportedly more likely to sustain their dog walking activity over time.48,49

However, not all dog owners actively walk their dogs.50 In an American survey (n=5,902) with 41% dog ownership, it was found that although ownership was associated increased regular physical activity, only 27% of dog owners actually walked their dogs and achieved the weekly recommended levels of exercise.50 Some studies have made a distinction in the role between pet
ownership and pet carers, and have reported that pet carers derived more physical activity-related health benefits than non-carers. Longitudinal studies with clinical measurements are needed to study the effect of the distinction between physical activity in dog carers vs dog owners. This would minimize the effects of response bias that may have been a feature in some of the aforementioned studies.

Variations in the amount of physical activity needed by different dog breeds also exist. A United Kingdom based survey (n=12,314) reported that the frequency of dog walking varied both within and amongst breeds, with several dogs not receiving the recommended amounts of exercise despite Kennel Club recommendations. The study did not investigate the physical activity levels of the owners, who may still have achieved adequate personal activity levels despite insufficiently exercising their dogs.

Dog ownership and hypertension

Hypertension is an important risk factor for cardiovascular and cerebrovascular morbidity and mortality. In the 2015 Global Burden of Disease report, hypertension was associated with the highest burden amongst the recorded risk factors accounting for approximately 211.8 million global DALYs.

Epidemiological evidence showing that dog ownership is associated with a lower risk of hypertension is inconsistent. An Australian cohort study (n=5,741) showed that systolic blood pressure and triglyceride levels were lower in dog owners than non-owners despite reporting similar body mass indices and smoking habits as non-dog owners. In contrast, an American cohort study (n=1,179) by Wright et al, showed no association between dog ownership and a lower blood pressure. An important limitation of this study was possible survival bias. The initial cohort (n=6,339), had been identified twenty years earlier and comprised a homogeneous group of participants. The study was designed to investigate associations with pet ownership and only reported the dog ownership results as part of a sub-group analysis.

Larger scale studies are needed to investigate the association between dog ownership and hypertension.

Dog ownership and dyslipidemia

Dyslipidemia is not commonly reported as an outcome in dog ownership studies. A cross-sectional study in 127 elderly Italian participants showed that pet ownership was associated with lower triglyceride levels, reporting better outcomes for dog owners, but also bemoaning the study’s low statistical power. In an Australian cohort study (n=5,741), male dog owners were found to have lower triglyceride levels than non-dog owners (6 mmol/l vs 7 mmol/l; p-value=0.01), but this difference did not remain after multivariable adjustment.
There was also no difference in plasma cholesterol levels between dog owners and non-owners (5.19 vs 5.17 mmol/l; p-value=0.78).\textsuperscript{55} Lentino \textit{et al}, in a cross-sectional study (n=916), showed that non-dog owners had 1.7 times the odds of hypercholesterolemia than dog owners even after adjustment for physical activity and age.\textsuperscript{56} When compared to the previous study, the study by Lentino \textit{et al}, suggests that in the presence of more confounding variables, there might be some benefit on the lipid profile of dog owners; however, this still needs to be determined.

\textbf{Dog ownership, obesity and diabetes mellitus}

There are inconsistencies in previous research findings on the association between dog ownership, obesity and diabetes mellitus. In the study by Anderson \textit{et al},\textsuperscript{55} there was no difference in body mass index (BMI) between dog owners and non-owners. In contrast however, in the cross-sectional study by Parslow \textit{et al} (n=5,079), pet owners were more likely to have a higher BMI, but similar rates of diabetes to non-owners.\textsuperscript{38} These studies were designed for pet ownership, and not only dog ownership.

When Lentino \textit{et al}, compared non-dog owners and owners in a cross-sectional study (n=916), the odds of diabetes were 2.5 times higher in non-owners than in owners.\textsuperscript{56} It was not possible to determine if prior poor health outcomes detracted participants from owning dogs or dog ownership was responsible for improving the health of the healthier dog-owning cohort.

Unlike the previous study, in a survey (n=1,179) Wright \textit{et al}, reported no difference in diabetes prevalence between dog owners and non-dog owners.\textsuperscript{54} There is thus no consensus on the prevention of diabetes mellitus status due to dog ownership in adults, and more studies need to be done.

\textbf{Dog ownership and psychosocial factors}

According to the INTERHEART study,\textsuperscript{5} psychosocial factors influencing CVD risk include acute life events, such as bereavement, depression, loneliness, locus of control and perceived stress at work or home.\textsuperscript{5} For the purpose of this thesis, only social support (which includes loneliness) and bereavement are discussed.

\textbf{Dog ownership and social support}

Dog ownership reportedly enhances the self-reported quality of life.\textsuperscript{19,57} Research shows that dog ownership offers intrinsic satisfaction for non-judgmental engagement in outdoor activities, spontaneity and relaxation.\textsuperscript{58} This companionship also has an extrinsic advantage in acting as a catalyst for interaction between strangers.\textsuperscript{19} Dog ownership enhances community integration between dog owners and non-owners alike, thus decreasing social isolation and feelings of loneliness, especially in urban settings.\textsuperscript{19,57} In an American survey
Garrity et al, showed that a strong pet attachment is associated with better health outcomes particularly when human support is less available. This was especially significant in bereavement where pet attachment buffered the impact of the death of a family member and resulted in a lower likelihood of loneliness and depression. No benefit of pet ownership in dealing with bereavement was found when the owner had one or more human confidants for support. These psychological advantages were disputed by Antonacopoulos et al, (n=132) who reported that pet owners with low levels of human social support experienced similar levels of loneliness and depression as non-pet owners who lived alone. There are however, few well-powered longitudinal studies investigating the importance of dog ownership and social support in those living alone.

**Pet bereavement and health outcomes**

In human-human relationships, the loss of a spouse has been associated with a higher excess all-cause mortality. In a Finnish longitudinal study (n=1,580,000) by Martikainen et al, the excess mortality for bereaved men was higher (17%) than that of women (6%) for all causes of death. Men were also more likely to die from CVD during the first 6 months (excess mortality 25%) after partner death, but this risk decreased during the next 6 months (excess mortality 15%). For women, the excess mortality from CVD was 25% in the first 6 months and only 8% in the 6 month period after.

Some mechanisms have been proposed to explain the association between bereavement (stress) and the development of acute and chronic disease, however, for the purposes of this thesis, only those related to CVD are discussed (Figure 1).

In the acute phase, exposure to stress triggers the release of cortisol and the stimulation of the sympathetic nervous system. This causes an increase in the heart rate and blood pressure. In addition, the myocardial demand for oxygen increases in the presence of transient myocardial ischemia. The ischemia, in the presence of an influx of macrophages, lipids and cytokines, may cause plaque disruption if plaques are present with resultant infarction, embolism or death. As the stress continues, endothelial dysfunction occurs and this decreases arterial compliance. Simultaneously, the body undergoes a series of pro-coagulation processes that increase platelet aggregation and a further likelihood for cardiovascular events.

Some individuals also have a sympathetic nervous system hyper-responsivity, which may also result in accelerated atherosclerosis in both the intermediate and long term.
Another important mechanism is behavioral change following bereavement. Changes in lifestyle may arise prior to the death of the spouse or in the immediate period after. Increased tobacco use, poor diet, increased alcohol consumption and physical inactivity, if sustained beyond the early grief period, may all predispose to obesity, worsening depression, hypertension and diabetes amongst other conditions, increasing long-term risk for CVD and death from any cause.

The death of a loved pet may also be associated with negative impacts on health. According to Testoni et al, individuals who consider their pet as a substitute attachment figure suffer from severe grief similar to the loss of a beloved person. In an Italian pilot study (n=159), the unexpected death of a pet was associated with higher scores of anger and grief, when compared to those who had anticipated the deaths, however, researchers concluded that their results were mostly speculative due to low statistical power. Apart from severe grief, which has previously been studied, the risk of cardiovascular disease and death from any cause after the loss of a pet is yet to be established.

Dog ownership and cardiovascular disease and death

The specific benefits of dog ownership on CVD was reported as early as the 1970’s, although few studies on this relationship have since been conducted. A heavily cited American cohort study investigated the one-year survival of patient’s post-myocardial infarction or angina pectoris. It was reported that out of the 92 patients followed up, survival was higher in pet owners (94%).
compared to non-owners (72%) even after adjustment for sex and marital status.68 An attempt to replicate these findings by Parker et al (n=424), found no difference in rates of cardiac death and readmission for dog owners and non-dog owners (21.9% vs 16.3%; p-value=0.249).69 Important differences between the two studies exist; the exclusion of participants with other serious comorbidities such as metastatic cancer, and restricting the analysis to the period after the first two months may have introduced a survivor bias. A study that replicates the first, whilst adjusting for serious co-morbidities on admission after acute myocardial infarction needs to be conducted.

Few studies have investigated the association between dog ownership and death from any cause.70 Two partly overlapping studies from the National Health and Nutritional Examination Study (NHANES II-III), reported no association between dog ownership and all-cause mortality. Although these two studies included quite high numbers of participants at baseline (n=590371 and n=396472), they both suffered from severe loss to follow up and methodological challenges that limit inference assumptions.71,72

In the recent Norwegian county population-based Nord–Trøndelag HUNT study, the death rate in dog owners was compared to that of non-owners (n=53,418).73 Dog ownership was not associated with mortality and this finding persisted in sex and age sub-group analyses. An important limitation of this study was that dog ownership was only measured at baseline and the long follow-up (median 18.5 years) did not account for the maximum lifespan of a dog (~10 years depending on breed), and lifestyle changes including socioeconomic factors, that may have occurred during the follow-up period.

The vast majority of studies that investigate the association between dog ownership and cardiovascular health have investigated associations with cardiovascular risk factors and not CVD outcomes.70 Longitudinal studies that address the association and distinguish between some important CVD outcomes are needed. Additionally, studies replicating and investigating the research on survival after established CVD are also needed.

Cardiovascular health in Sweden

Sweden has a population of approximately 10 million. In 2010, it was estimated that 18% of Sweden’s residents were aged 65 years or older - a proportion that continues to increase as the average life expectancy rises.74 Cancer and CVD are the two most important causes of death in Sweden. In 2010, death from cancer was more common than death from CVD for women and men aged 65-74, but amongst those aged ≥ 75 years, CVD remains the predominant cause of death.75

Cardiovascular disease is associated with a high cost-to-care and in 2015, the total healthcare cost for CVD in Sweden was in excess of 1.6 million Euros. The age-standardized prevalence rate for CVD decreased between 1990 to
2015 from 4,798 to 4,507 per 100,000 but still remains high and more measures to reduce this rate are needed.\(^4\)

The overall health of Swedish adults has improved remarkably with lower smoking rates, lower alcohol consumption and earlier detection and treatment of disease in the last two decades.\(^{74,75}\) However, despite improved public health awareness, there has been a steady increase in the number of obese people in Sweden.\(^76\) Physical activity during leisure time is more common among women than men but in general, the proportion of the population who achieve at least moderate levels of activity has declined in recent years.\(^77\) With an increasingly ageing population, many elderly individuals remain in their homes beyond the age of 80 and receive assisted care where necessary.\(^75\) This means that apart from improving diet and physical activity levels; measures that reduce social isolation, feelings of loneliness and improve locus of control all continue to be important.

**Dog ownership in Sweden**

In 2012, there were approximately 780,000 registered dogs in Sweden.\(^78\) Strict legislation governs animal welfare, including conditions of dog ownership. Since 2001, each dog must be registered with the Swedish Board of Agriculture before 4 months of age or at change of ownership and de-registered at death. Dogs are labelled by either an ear tattoo or a subcutaneous micro-identity chip. Registration insures easy identification of the owner via a linked personal identity number and this means that finding stray dogs is virtually impossible as owners can easily be traced by authorities.\(^{58,78}\)

There is also direct guidance for the frequency of daily physical activity of both companion and farm dogs, the size of dog living spaces, transportation and nutrient intake, amongst other things.\(^58\) Recommendations state that dogs be exercised every 6 hours and farm dogs allowed to exercise in an environment different to their regular enclosure at least once a day.\(^58\) In Sweden compliance to pet ownership regulations is thought to be high due to a general high level of social and institutional trust.\(^79\)
Rationale for Current Work

Whilst research investigating the effects of dog ownership is prevalent in scientific literature, study findings have been contradictory and difficult to replicate. A statement released by the American Heart Association in 2013 concluded that dog ownership likely reduced the risk of CVD but at the same time bemoaned the methodological issues employed by the most commonly referenced studies. 

Inconsistencies may be in part due to low statistical power in small studies, use of restricted or homogenous populations, failing to adjust for important socio-economic confounders, inability to account for different types of pet (cat or dog), dog breeds, or simply an absence of effect. Additionally, several studies are conducted in geographically uniform areas and employ study and analytic methods that make generalizations to other populations a challenge. Furthermore, there are no studies investigating the relationship between pet loss and CVD and all-cause mortality, despite studies reporting pet attachment and substitutive companionship in some owners.

Project objectives

The main aim of this research project was to investigate the impact of dog ownership on human cardiovascular health and all-cause mortality, using the unique Swedish population and health registries available for humans as well as for pet animals.

Specific aims

The specific aims of this project were:

I to assess the association between dog ownership with CVD and all-cause mortality (Study I)

II to assess the association of dog ownership with initiation of treatment for the CVD major risk factors hypertension, dyslipidemia and diabetes mellitus (Study II)

III to clarify the association between dog ownership and mortality after a major cardiovascular event (Study III)
IV to explore how the death of a pet (cat or dog) affects the acute CVD risk in the owner (Study IV)
Materials and Methods

This thesis builds on linked extracts from a number of Swedish population and health registers, two national dog registers as well as an extract from the animal-insurance company Agria insurance. In two of the papers, data from a separate linkage of the Swedish Twin register and the dog registers are included.

The Personal Identity Number

Since 1947, it has been a statutory requirement for every Swedish resident to be registered by a unique identifier called the personal identity number (PIN). This unique identifier makes it possible to link information across a number of different population registers for both administrative and research purposes.80

Table 1. Databases used in this project

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The Swedish Population and Health Registers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Register of the Total Population</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>The Longitudinal Integration Database for Health Insurance and Labor Market Studies</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>The Swedish National Patient Register</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>The Swedish Prescribed Drug Register</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Swedish Cause of Death Register</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>The Swedish Twin Registry Cohorts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Screening Across the Lifespan Twin study</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TwinGene</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>The Pet Registers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Swedish Kennel Club Register</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>The Swedish Board of Agriculture Dog Register</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>The Agria Pet Insurance Registry</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
The Swedish Population and Health Registers

Register of the Total Population

Sweden has a long tradition of registering the population. The Register of the Total Population (RTP) started in 1968 with the aim of providing a structured system with which to obtain data that reflected the composition and identities of the Swedish population. This database is an administrative tool that contains information on all Swedish citizens and residents. It contains individual level information including the PIN, name, sex, place of birth, citizenship, family status, place of residence, migration and death dates. Whilst emigration and re-entry do not affect one's PIN, ideally individuals must de-register if they intend to live outside of Sweden for ≥1 year. This is not consistently done and it is estimated that the Register of the Total Population has an over-coverage of between 0.25% - 0.5% arising mainly from foreign-born migrants who do not deregister upon departure.

The Longitudinal Integration Database for Health Insurance and Labor Market Studies

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) is a derivative of the Total Population Register. Since its initiation in 1990, the database has included information on all registered residents aged ≥16 years on the 31st of November annually. It integrates person specific variables on educational attainment and labor market and social sector involvement. It also incorporates family, health insurance and workplace information.

The Swedish National Patient Register

The National Board of Health and Welfare has kept records of individual hospital discharges since 1964. By 1987, this administrative database had expanded to achieve nationwide coverage of all somatic and psychiatric hospital discharges. Since 2001, the register includes all specialist outpatient visits, day-surgeries and psychiatric care from both private and public healthcare providers. The register includes three categories of patient information: i) patient data including PIN, gender and age, ii) the geographic location of the hospital including the department details and iii) administrative data such as the date of admission and discharge, the main and subsidiary diagnoses using the ICD codes, length of stay and all procedures performed. Inpatient coverage is almost 100% and outpatient coverage is approximately 87%, with both public and private caregivers reporting to this register. It does not contain any information on the medical treatment provided during a patient’s hospital stay.
The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register has covered dispensed drugs at Swedish pharmacies since July 1st 2005. This population-based register contains information on the Anatomical Therapeutic Chemical (ATC) classification of the prescribed drug, dosage, quantity and strength. It also provides information on the PIN, age, sex, prescriber and associated costs. The drug name and date of prescription provide a good proxy for the disease category and the date of disease diagnosis, respectively. A new prescription that was preceded by a long enough period without a prescription can be seen as a proxy of disease diagnosis.

The Cause of Death Register

Established in its current form in 1952, the Swedish Cause of Death Register is an official administrative register compiled by the National Board of Health and Welfare. It contains detailed information on the death details of Swedish residents occurring both in Sweden and abroad. The Cause of Death Register includes ICD-coded information on the main cause of death and all contributing causes. When cause of death information is missing on a death certificate, deaths are reported without a cause of death. In 2015, 0.9% of all the deaths reported lacked information on the cause of death.

The Swedish Twin Registry

The Swedish Twin Registry is a population-based national register of Swedish twins initially started in the late 1950’s for the purposes of research and is managed by researchers at Karolinska Institutet. It contains information about more than 194,000 twins in Sweden derived from the twins, their partners or parents, and linked to the national population and health registers. There are several different sub-cohorts within the Swedish Twin Registry, however, only the two used in this project are described:

The Screening Across the Lifespan Twin (SALT) study

This study, conducted between 1998 and 2002 had the objective to include all twins born before 1958 from the Swedish Twin Registry. Data on 44,914 twins was collected using a computer-assisted telephone interview performed by trained interviewers. Individual information such as data on behavior and lifestyle, occupation, and permission to link personal information to other population registers was obtained. Linkages were then performed with the national health and population registers.
TwinGene

TwinGene is a nested cohort within the SALT study. Conducted between 2004-2008, it was primarily created to study the molecular influences on common diseases, and contains information on 12,614 twins born between 1911 and 1958. Health data were collected from questionnaires and blood sampling material was mailed to the subject who then contacted a local healthcare centre for blood sampling and a health check-up. Participants were instructed to fast from 8pm the night prior to a healthcare center visit. At the facility, a simple health check was performed after a 5 minute rest period with measures including systolic and diastolic blood pressure, weight, height, hip and waist circumference. Blood was then collected for DNA extraction and stored. Clinical blood assessments were made for total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, hemoglobin A1c, C-reactive protein and glucose amongst other biomarkers.

The Pet Registers

The Swedish Kennel Club

The Swedish Kennel Club (SKK) was founded in 1889. It is the sole kennel club in Sweden and is specifically concerned with the welfare of purebred dogs. Approximately 90% of Sweden’s pure bred dogs are registered here and thus it provides the most complete means for assigning breed codes to the whole national canine population. Information collected by Swedish Kennel Club on each dog includes dog breed, name, a unique subcutaneous chip ID or tattoo number, date of birth, changes in ownership and date of death. The owner’s PIN is also registered.

The Swedish Board of Agriculture Dog Register

The Swedish Board of Agriculture is the main authority for official statistics on the agricultural sector and aquaculture in Sweden. Although it has provided statistics since 1965, it has only been a statutory requirement to have all dogs registered and identified by either tattoo or microchip identification since 2001. Dog registration must be performed within the first 4 months of life, or at purchase by the new owner. Information collected includes the owner’s PIN, dog name, chip identification number or tattoo number, dog breed, sex and date of birth. Changes in ownership, dog name and death must also be reported as soon as possible. To ensure full coverage, questionnaires that include vital status information about the dog are sent out every year.
The Agria Pet Insurance Registry

Agria Pet Insurance (*Agria Djurförsäkring*) is the largest private-owned animal insurance company in Sweden. In general, Sweden has extremely high standards for responsible animal ownership. In 2006, 78.4% of all dogs and 26.9% of cats were insured, with Agria Pet Insurance hosting approximately 50% of all insured dogs.

There are two broad types of insurance provided: veterinary care insurance and life insurance. Veterinary care insurance provides cover for regular veterinary care and treatment above the amount paid out of pocket by the policy holder. This cover lasts approximately 12 years. Life insurance can be taken for dogs aged less than 6 years, and depending on the breed of the dog cannot exceed 10 or 12 years.

This pet insurance registry is suitable for epidemiological research and reflects the Swedish dog population in terms of sex, age and breed, but this reflection does not extend to the mixed pedigree dogs and those aged >10 years.

Ethical approval

The thesis projects were approved by the Regional Ethical Review Board in Stockholm, Sweden (diary number 2012/1114-31/2, with an amendment registered 2013-1687-32). An additional ethical approval was obtained for the Swedish Twin Registry to include the TwinGene: number 2007/644-31/2 and 2016/1392-31/1).

All data from the major register linkage was anonymized by Statistics Sweden and National Board of Health and Welfare prior to being made available to the researchers. Similar procedures were undertaken at the Karolinska Institutet before delivery of data from the Swedish Twin Registry.

Written informed consent was provided by twins in TwinGene when participating in the TwinGene study and was not needed for the purpose of this research project.

Data security

Data protection was ensured by using secure infrastructure provided by the National Bioinformatics Infrastructure Sweden. The system meets the standards regulated in the European Union General Data Protection Regulation.
Main exposures, outcomes and confounders

Exposures

Dog ownership

Dog ownership was the main exposure in Study I, Study II and Study III.

It was defined as registered ownership in either the Swedish Kennel Club or Swedish Board of Agriculture dog registers, or having a spouse/partner registered as a dog owner in either register.

In Study I and Study II, dog ownership was time-updated allowing us to define periods of ownership and periods when dog owners were considered non-owners (Figure 2).

In Study III, dog ownership was defined as registered ownership at time of diagnosis of either acute myocardial infarction or ischemic stroke.

Some limitations to defining the exposure were encountered. Firstly although Swedish legislature mandates dog registration, it is possible that some owners had not registered, and some dogs were not de-registered at death. There was information on dog death available in the Swedish Kennel Club dog register, but this information was incomplete in the Swedish Board of Agriculture register. Where this information was missing, we assumed a maximum lifespan of 10 years for the dog based on a 2012 Statistics Sweden report on dogs, cats and other pets. The report showed that approximately 88% of dogs in the population are aged<10 years. Secondly, the Swedish Twin Registry had no partner personal identification numbers available and thus dog ownership was restricted to the index person, and lower than that in the national cohorts.

Pet loss (pet bereavement)

Pet loss or bereavement (both dog and cat) was the main exposure in Study IV.

Pet owners were identified from the Agria Pet Insurance Registry between January 1st, 2004 and December 31st, 2012. Exposure was defined as having a pet die within the time study period. Only pets with life-insurance were included. This was necessary as pet de-registration at death or at discontinuation of insurance cover is more likely in participants with life- than veterinary-care insurance only.
Breed groups
Breed groups analyses were included to investigate the relationship between the particular breed groups and the related outcomes in Study I, II and III.

Ten breed groups were defined using the Federation Cynologique International standard with some local adaption from the Swedish Kennel Club.95 The categories are based on appearance, character and behaviour. An additional 11th group comprising all mixed-pedigree dogs was also created.

Outcomes

Cardiovascular disease and death
Cardiovascular disease and death from any cause were outcomes in Study I, III and IV.

Records with ICD-codes were extracted from the National Patient and Cause of Death Registers. Each outcome was defined as a main diagnosis of the following: acute myocardial infarction (ICD-10 I21), ischemic stroke (ICD-10 I63), hemorrhagic stroke (ICD-10 I60-I62) and heart failure (ICD-10 I50). The presence of one of these was also enough for a diagnosis of composite-CVD/ major acute cardiovascular event (MACE).

In Study I, the main outcomes were acute myocardial infarction, ischemic stroke, hemorrhagic stroke, heart failure. In addition, composite-CVD, death from composite-CVD and death from any cause were also included as outcomes.
In Study III, the main outcome was death from any cause; however, a main diagnosis of acute myocardial infarction or ischemic stroke was used to identify two independent study populations.

In Study IV, the main outcome was a MACE; repeated events were also allowed.

Validation studies of the Swedish Inpatient Register have estimated the sensitivity of the diagnosis of acute myocardial infarction at 91.5% 34 (a proportion that increases when outpatient care is included), and ischemic heart disease at 80.5%. 34 According to validation studies conducted on this register, the positive predictive values of the in-patient diagnoses were 85-95% for most diagnoses. 83

In Study I and III, death from any cause was identified from the Cause of Death Register. Overall, 96% of individuals in the Cause of Death Register have a specific underlying cause of death recorded. The majority of those with missing data died abroad. 86 Diagnoses in this register have a high level of correlation with hospital records, ranging between 83% and 97% in ischemic heart diseases and up to 98% is cerebrovascular related conditions. 96

Cardiovascular risk factors
In Study II, cardiovascular risk factors, including hypertension, dyslipidemia and diabetes mellitus, were used as outcomes. As a proxy for each outcome, initiation of treatment for any of the three conditions was extracted from the Swedish Prescribed Drug Register using the Anatomical Therapeutic Chemical Classification System (ATC) codes.

A 15-month ‘washout’ period was given between the start of the drug register on July 1st, 2005 and the start of the study on October 1st, 2006. This period was used to exclude anyone with a prescription with the conditions of interest.

Anti-hypertensive medication was defined as medication with the following with ATC-codes: C02 (antihypertensive drugs), C03A, C03EA01 (thiazide diuretics), C07 (beta-receptor blockers, excluding sotalol [C07AA07]), C08C (selective calcium antagonists with mainly vascular effects) and C09 (agents acting on the renin-angiotensin system).

Lipid-lowering (dyslipidemia) medication as drugs with ATC-codes: C10AA (statins), C10AB (fibrates), C10AC (bile acid sequestrants), C10AX (other lipid-modifying agents) and C10B (lipid-lowering drug combinations).

Glucose lowering (diabetes mellitus) medication as drugs with ATC-codes: A10A (insulin and analogues) and A10B (glucose-lowering drugs excluding insulin).

The Swedish Prescribed Drug Register provides complete national data on the number of individuals exposed to dispensed drugs in the Swedish population. 84 However, it is limited in not providing any information on the underlying diagnosis, medications administered during a hospital admission, medications dispensed without a prescription or those used in a nursing home. 84
register had 84% national coverage of the total volume of drugs consumed in 2006,\textsuperscript{84} and this has increased significantly in recent years.\textsuperscript{85} The highest proportion of the utilization included in the register was observed for cardiovascular drugs (98% of the defined daily doses and 96% of expenditures).\textsuperscript{84}

**Potential confounders**

A confounder is traditionally defined as a variable that may account for a part of, or all of, the association between an exposure and the outcome of interest.\textsuperscript{97} To minimize the effect of confounding, we applied the theoretical structured ordering of factors by use of directed acyclic graphs (DAG). They are primarily used to encode researchers’ \textit{a priori} assumptions about the relationships between and among variables in causal structures.\textsuperscript{98,99}

**Common confounders**

Information on age, sex, marital status, region of birth, area of residence, level of education, household income, population density and latitude of residence was obtained from the annual updates from the Register of the Total Population.

Marital Status was included as married/cohabiting, single, divorced or widowed. Study participants were considered married /cohabiting if they were registered as married, living in a registered (same-sex) partnership or cohabiting with children in common, whether or not the children were living in the home.

Level of education was divided into three categories (compulsory level, \(\leq 9\) years. Secondary level, \(10-11\) years or tertiary level \(\geq 12\) years). This information was only available for participants aged \(\leq 75\) years in 2001. This is based on administrative procedures done annually by Statistics Sweden.

Latitude of residence was included to account for the differences in the north-to-south factors associated with access to health care and clustering of CVD. Rajabi et al, showed in a recent study that there are spatially clustered patterns in the distribution of CVD in Sweden.\textsuperscript{100} Higher CVD hospital admissions are reported for men in the northern parts, as well as some parts of central Sweden, and their lowest admissions on the western parts of the country. Conversely for women, the highest areas of admission were in the northern parts of the country and the lowest admission and prevalence rates in the Southern parts of the country.\textsuperscript{100}

**Charlson comorbidity index**

The Charlson comorbidity index was used in the main analyses in Study III and as part of the sub-cohort Twin analyses in Study I and Study II. As a validated measure of frailty, it accounts for the burden of disease and predicts the ten-year mortality risk on admission. The index includes a list of 17 categories of comorbid conditions (pre-existing or occurring during the clinical
course of a patient with a primary disease of interest). Each category is assigned a weight from 1 to 6 for mortality risk and disease severity. Index scores ≥5 are associated with a one-year mortality of 85%.101,102

In Study I and II, comorbid conditions were obtained from patient information in the Swedish Twin Register and from the subsidiary diagnoses of the Swedish National Patient Register in Study III. In Study III, we modified the index to exclude myocardial infarction or ischemic stroke as they were used to define the study population.

The national registers did not have information on important confounders such as tobacco use, BMI, level of physical activity or functional ability. However, by using the two sub-cohorts from the Swedish Twin Registry – SALT and TwinGene, we were able to adjust for these confounders in a smaller population and replicate our findings (Study I and III) in a subset of the total population.

**Living alone**

Living alone (single-person household) or living with someone (multiple-person household) was used as stratification variable in all four studies. Participants were assigned as living alone if registered as living alone. They were assigned to living with someone if they were married, living with a partner or a child. It was not possible to trace non-married partners in the registers if the couple had no children together.
Study Summaries

Study designs and methods
An overview of each of the Studies, I – IV, is presented in Table 2.
Table 2. Overview of the design and methods for Study I-IV

<table>
<thead>
<tr>
<th>Study</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Population-based observational</td>
<td>Population-based observational</td>
<td>Population with myocardial infarction or ischemic stroke</td>
<td>Population-based observational</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>1). 3,432,153 adults (13.1% dog owners), aged 40-80 years, CVD-free at study start, followed 2001-2012 2). 34,202 adults from Twin Register (8.5% dog ownership) aged 42-80 years followed 2001-2014</td>
<td>1). 2,026,865 adults (14.6 % dog owners), aged 45-80 years, CVD-free; at study start, followed 2006-2012 2) 10,110 adults (5.0% dog ownership) from the TwinGene cross-sectional study adjusting for lifestyle factors</td>
<td>181,696 (6% dog owners) with first-in-life acute myocardial infarction and 154,617 adults (5% dog owners) with ischemic stroke, aged 40-85 years; study start from January 1st 2001 and followed up to death, emigration or study end December 31st 2012</td>
<td>147,251 cat and dog owners with active life insurance in the Agria insurance database at any point between January 1st 2004 and December 31st 2012 were included. Pet loss was experienced by 30,865 (21.0%) of the population</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td>Dog ownership</td>
<td>Dog ownership</td>
<td>Dog ownership</td>
<td>Loss-of-a-pet</td>
</tr>
<tr>
<td><strong>Independent Outcome Measures</strong></td>
<td>Incident heart failure, acute myocardial infarction, hemorrhagic stroke, ischemic stroke, composite CVD, cardiovascular death, all-cause death</td>
<td>Incident hypertension, dyslipidaemia and type 2 diabetes using the Prescribed Drug Register as a proxy for disease surveillance</td>
<td>All-cause death</td>
<td>Major acute cardiovascular event</td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td>Survival analysis</td>
<td>Survival analysis (in main cohort) and logistic and linear regression (in twin cohort)</td>
<td>Survival analysis and logistic regression</td>
<td>Survival analysis and flexible parametric models to assess risk continuously over time after pet death</td>
</tr>
</tbody>
</table>
Study I

Dog ownership and the risk of cardiovascular disease and death – a nationwide cohort study

The association between dog ownership and incident CVD and death from all cause was investigated in a Swedish population-based prospective cohort. Individual-level data for Swedish adults aged 40 to 80 years (n=3,432,153) was extracted from the Register of the Total Population in 2001 and linked to dog ownership registers.

Cohort participants were free from cardiovascular disease on study onset, which was ensured by excluding anyone with a history of CVD in the National Patient Register (ICD-9 codes 390–459 or ICD-10 I00-I99; main or secondary diagnosis) and/or had a coronary artery bypass grafting or percutaneous coronary artery intervention (Nordic surgical procedure codes FNA, FNC and FNG). All cohort members were followed through national population and health registers to the date of CVD diagnosis (defined as acute myocardial infarction, ischemic stroke, haemorrhagic stroke, heart failure, or a composite of these outcomes), date of death (from composite-CVD or all-cause death), date of emigration, or end of follow-up (December 31st 2012), whichever came first.

Cox proportional hazards regression was used for time-to-event analyses. Hazard ratios and 95% confidence intervals were calculated in both sex and age adjusted models, as well as models adjusted for age, sex, marital status, presence of children in the home, population density, area of residence, region of birth, income and latitude of residence.

An additional sub-cohort with more confounders was extracted from the Swedish Twin Register and additional covariates including body mass index, tobacco use, Charlson comorbidity index, employment status and level of exercise were adjusted for.

Study II

Dog ownership and cardiovascular risk factors: a nationwide prospective register-based cohort study

The association between dog ownership and time to initiation of medication for three major cardiovascular risk factors was studied in a nationwide prospective cohort. All CVD-free Swedish adults aged between 45 to 80 years on October 1st 2006 (n=2,026,865) were extracted from the Register of the Total Population and linked to registers the Swedish Kennel Club and Swedish
Board of Agriculture registers for dog ownership (n=295,682; 14.6%). Individuals with a history of using medication for either hypertension, dyslipidemia or diabetes mellitus were excluded from July 1st 2005 to October 1st 2006 to prevent including participants with long standing drug prescriptions.

The cohort was then followed through the Swedish Prescribed Drug Register for time to initiation of medication for hypertension, dyslipidemia and diabetes mellitus as independent outcomes and censored at death, emigration or study end on December 31st 2012. In addition, censoring was also done at a diagnosis of heart failure, unstable angina and/or myocardial infarction for those initiating treatment for hypertension and lipid modifying medication. This was done as some medications used to treat our outcomes of interest overlapped with them.

Cox proportional hazards regression was used for time-to-event analyses. Hazard ratios and 95% confidence intervals adjusted for age, sex, marital status, presence of children in the home, population density, area of residence, region of birth, income, education level and latitude of residence were then calculated.

Furthermore, a cross-sectional analysis was performed from a sub-cohort derived from the Swedish Twin Register with additional variables (n=10,110). Dog ownership was identified using the Swedish Kennel Club and Swedish Board of Agriculture registers (n=484; 5%). By using logistic regression analyses, odds ratios and 95% confidence intervals were obtained for the independent prevalent use of medications for hypertension, dyslipidaemia and diabetes mellitus. Models were adjusted for sex, age, number of children in the home, area of residence, population density, marital status, tobacco use, occupational level, employment status, disability and Charlson comorbidity index.

Study III

Dog ownership and mortality after a major cardiovascular event – a register-based prospective study

The association between dog ownership and mortality after a major cardiovascular event was investigated in a population-based nationwide cohort study. Using the Swedish National Patient Register, all patients with a first ever myocardial infarction (n=181,696) or ischemic stroke (n=157,617) between January 1st 2001 and December 31st 2012 were identified. Individuals were then linked to the Swedish Kennel Club and Swedish Board of Agriculture registers for dog ownership (acute myocardial infarction n=10,287; 5.7% dog ownership and ischemic stroke n=7,344; 4.8% dog ownership, respectively). Additional linkage to the Registers for the Total Population and Cause
of Death for socioeconomic indicators and outcomes, respectively, was then done.

Cox proportional hazards models were used to evaluate the association of dog ownership at time of CVD diagnosis with time-to-death during follow-up using attained age as the time-scale. Participants were censored at emigration or end of study on the December 31st 2012. The resultant hazard ratios and 95% confidence intervals were adjusted for age, sex, marital status, presence of children in the home, population density, area of residence, region of birth, income, Charlson comorbidity index and latitude of residence; all measured at the day of the CVD event. Adjusting for the same covariates, logistic regression modelling was also used to assess the odds of dog ownership and survival at one-year after a myocardial infarction or ischemic stroke independently.

Study IV

The impact of death of a pet on major acute cardiovascular risk in the owner: a register-based cohort study

The aim was to study the association between the death of a pet on the risk of a major acute cardiovascular event (MACE; defined as a composite outcome of acute myocardial infarction, ischemic stroke, hemorrhagic stroke and heart failure) or death of the owner due to MACE. We identified the population of life insured pets (both cats and dogs) from the Agria Pet Insurance register between January 1st 2004 and December 31st 2012 (n=147,251). This was linked to owner longitudinal data from the National Patient and Cause of Death registers.

Exposure (pet death) was experienced by 30,865 (21.0%) pet owners with 116,386 (79.0%) not experiencing loss. The risk of a MACE in different time windows close to the date of loss to the risk of MACE during the reference period (>12 months before loss or no loss). The time windows are shown in Table 3:

<table>
<thead>
<tr>
<th>Time Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 12 months before loss (reference)</td>
</tr>
<tr>
<td>6-12 months before loss</td>
</tr>
<tr>
<td>3-6 months before loss</td>
</tr>
<tr>
<td>3 months before loss (excluding the last week)</td>
</tr>
<tr>
<td>Week before loss</td>
</tr>
<tr>
<td>Week after loss</td>
</tr>
<tr>
<td>3 months after loss (excluding first week)</td>
</tr>
<tr>
<td>3-6 months after loss</td>
</tr>
<tr>
<td>6-12 months after loss</td>
</tr>
</tbody>
</table>

Table 3: Time intervals before and after pet death
Individuals were censored 12 months after the date of death of the pet. In addition, pet owners were censored when their insurance subscription was terminated for reasons other than pet loss (e.g. pet too old for renewing the policy). To exclude the time period potentially right before a non-recorded pet loss, we additionally censored pet owners 12 months before the end of the subscription or on December 31st 2011, whichever came first, to exclude the time period potentially right before a non-recorded pet loss.

Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals for MACE events in the different time intervals around the death of the pet compared to the reference period using attained age as the time-scale. Models were adjusted for sex, region of birth and area of residence. In addition, a history of any CVD was added as a time varying covariate.

Flexible parametric survival methods to estimate the time-specific hazard ratios of MACE was then performed. Individuals with pet loss were compared against those without pet loss during the 12 months after loss. This method enabled the examination of time-related fluctuations of the risk of MACE after the loss of a pet. Each pet-loss exposed individual (index pet loss) was matched on sex, age, pet birth year and pet breed to 5 non-exposed individuals using incidence density sampling. Where it was not possible to match with 5 non-exposed individuals, 4 non-exposed individuals were used instead. We used time since pet loss as a time scale and five and three degrees of freedom for modelling the baseline hazard and time-dependent effect of pet loss, respectively. The non-exposed individuals’ pets had to be alive and to be life-insured at the time of the index pet loss. Models were adjusted for the matching factors (sex and age of the owner at date of loss, pet breed and birth year), region of birth, and area of residence and age of the pet at the matching date.
Main Results

Study I

In this national cohort study (n=3,432,153), we observed that dog ownership was associated with a lower risk of death due to composite-CVD (multivariable adjusted-HR 0.77, 95% CI, 0.73-0.80). Dog ownership was also associated with a lower risk of all-cause death (multivariable adjusted-HR 0.80, 95% CI, 0.79-80).

In stratified analyses, effect measure modification was observed for single-person households for every outcome except haemorrhagic stroke. In single households, dog ownership was associated with an inverse association with incident CVD, as well as with a stronger inverse association with composite CVD-death and all-cause death compared to multiple person households Figure 3. Age category also modified the association between dog ownership and the risk of acute myocardial infarction, particularly in the older age groups.

Breed group analysis showed that owning a mixed pedigree dog was associated with an increased risk of composite-CVD (multivariable-adjusted HR, 1.13, 95% CI, 1.09–1.17), and dogs originally bred for hunting, including the terriers, retrievers, pointing dogs, scent hounds and related dogs, all showed reduced risk of composite-CVD (HR, 0.87-0.97).

In the twin cohort (n=34,202), we observed wide confidence intervals but with estimates overlapping the null (composite-CVD HR, 1.09 95% CI, 0.92–1.28), and all-cause mortality (multivariable-adjusted HR 0.89 95% CI 0.73–1.09). Adjustment for additional confounders including BMI, smoking, Charlson comorbidity index, employment status and level of exercise had no large effects of the estimations.
Figure 3. Hazard ratios and confidence intervals of the associations between dog ownership and CVD outcomes in the National cohort stratified by household type, age category and sex.
Study II

In this national cohort study (n=2,026,865), we found that dog ownership was associated with an approximately ~2% higher risk of initiation of anti-hypertensive or lipid-modifying medication; whereas no overall association was observed between dog ownership and initiation of blood glucose lowering medication.

In stratified analyses, effect modification was observed for those aged <50 years who were at increased risk for initiation of anti-hypertensive and lipid-modifying medication (HR, 1.04; 95% CI, 1.01-1.08 and HR, 1.10; 95% CI, 1.04-1.15, respectively), with elevated risks attenuated with increased age. Effect measure modification was also observed in those initiating blood-glucose lowering medication with reduced risks in those in lower age groups (HR, 0.89; 95% CI, 0.79-0.99), in males (HR, 0.95; 95% CI, 0.92-0.99) and in those who were not living alone in their household (HR, 0.91; 95% CI, 0.86-0.97) (Figure 4).

Breed group analysis showed that owning a mixed pedigree dog was associated with an increased risk of initiating treatment for hypertension, dyslipidaemia and diabetes mellitus. Dog owners with a dog previously bred for hunting had, in contrast, a lower risk of initiating treatment for diabetes mellitus.

In the twin cohort (n=10,110), we observed that after adding the additional confounders, including employment status, Charlson comorbidity index, disability and tobacco use, estimates were fully attenuated, indicating presence of remaining confounding in the national cohort analysis.
**Figure 4.** Hazard ratios (HR) and 95% confidence intervals (CI) for the association of dog ownership and time to initiation of medication for hypertension, dyslipidaemia and type 2 diabetes. Models presented were stratified by age category, sex and home occupancy status (living alone or with someone). Adjustment was for age, sex, marital status, presence of children in the home, population density, area of residence, education level, region of birth, income and a correction for latitude of residence (with age, sex, marital status and presence of children at home excluded for the relevant stratified model).
Study III

In this national prospective cohort including all Swedish residents diagnosed with a myocardial infarction (n=181,696) between January 1st, 2001 and December 31st, 2012. We found that owning a dog at diagnosis was associated with a 24% reduction in overall mortality compared with individuals who did not own a dog. The odds of death by one year after diagnosis were also lower in dog owners (adjusted OR, 0.72; 95% CI 0.67-0.78).

Similarly, in the cohort consisting of all index ischemic stroke events (n=154,617), all-cause mortality was significantly lower in dog owners than in non-owners (multivariable-adjusted HR, 0.80; 95% CI 0.76-0.84). The one-year odds of death was also lower in dog owners (adjusted OR, 0.77; 95% CI 0.71-0.84).

In stratified analysis, the association of dog ownership with mortality was stronger for single-person households than those in who patients did not live alone in both those with an index myocardial infarction event and an index ischemic stroke, (multivariable-adjusted HR, 0.65; 95% CI 0.59-0.72 and HR, 0.72; 95% CI 0.65-0.79) respectively (Figure 5).
### Outcome

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard ratio (95% CI)</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Myocardial Infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude model (Non-stratified)</td>
<td>0.71 [0.67, 0.74]</td>
<td>69,232</td>
</tr>
<tr>
<td>Fully-Adjusted Model (Non-stratified)</td>
<td>0.76 [0.73, 0.80]</td>
<td>69,232</td>
</tr>
<tr>
<td>&lt;65 yrs</td>
<td>0.85 [0.78, 0.93]</td>
<td>7,454</td>
</tr>
<tr>
<td>65-75 yrs</td>
<td>0.79 [0.73, 0.85]</td>
<td>16,817</td>
</tr>
<tr>
<td>75-85 yrs</td>
<td>0.70 [0.65, 0.77]</td>
<td>44,961</td>
</tr>
<tr>
<td>female</td>
<td>0.74 [0.67, 0.81]</td>
<td>27,922</td>
</tr>
<tr>
<td>male</td>
<td>0.77 [0.73, 0.82]</td>
<td>41,310</td>
</tr>
<tr>
<td>living alone</td>
<td>0.65 [0.59, 0.72]</td>
<td>33,662</td>
</tr>
<tr>
<td>not living alone</td>
<td>0.82 [0.78, 0.87]</td>
<td>35,570</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude model (Non-stratified)</td>
<td>0.76 [0.72, 0.80]</td>
<td>67,227</td>
</tr>
<tr>
<td>Fully-Adjusted Model (Non-stratified)</td>
<td>0.80 [0.76, 0.84]</td>
<td>67,227</td>
</tr>
<tr>
<td>&lt;65 yrs</td>
<td>0.84 [0.78, 0.94]</td>
<td>5,556</td>
</tr>
<tr>
<td>65-75 yrs</td>
<td>0.81 [0.75, 0.88]</td>
<td>15,432</td>
</tr>
<tr>
<td>75-85 yrs</td>
<td>0.80 [0.73, 0.86]</td>
<td>46,239</td>
</tr>
<tr>
<td>female</td>
<td>0.82 [0.75, 0.89]</td>
<td>31,680</td>
</tr>
<tr>
<td>male</td>
<td>0.80 [0.75, 0.86]</td>
<td>35,547</td>
</tr>
<tr>
<td>living alone</td>
<td>0.72 [0.65, 0.79]</td>
<td>34,482</td>
</tr>
<tr>
<td>not living alone</td>
<td>0.85 [0.80, 0.91]</td>
<td>32,735</td>
</tr>
</tbody>
</table>

**Figure 5.** Hazard ratios and 95% confidence intervals for the association of dog ownership with time to death after acute myocardial infarction or ischemic stroke. Non-stratified results and results stratified by age, sex and living alone or not in the home adjusted for age, sex, marital status, children in the home, latitude of residence, region of birth, income, modified weighted Charlson comorbidity index and a history of previous cardiovascular events prior to the index event are shown. The crude model was sex- and age adjusted.
Study IV

In this cohort of life-insured pet owners (n=147,251; 9.0% cats and 91.0% dogs) were included. Pet loss was experienced by 30,865 (21.0%) of the insured pet owners between January 1st, 2004 and December 31st, 2011; and the risk of CVD or mortality due to a major cardiovascular event relative to the period 12 months before pet death compared

In both age and sex–adjusted, and adjusted for age, sex, country of birth, area of residence and marital status, the risk of MACE was higher one week after loss, 3 to 6 months after loss and 6-12 months after pet loss Figure 6.

Figure 6. Hazard ratios (HR) and 95% confidence intervals (CI) for the sex and age-adjusted and fully-adjusted models for the association of pet loss and risk of a major acute cardiovascular event in different time intervals before and after pet loss.
On stratified analysis, women had a higher risk of MACE during the first week after loss, whilst men had a higher risk 3 months after pet loss.

Similar to the cohort analysis, the time-related fluctuations after the loss of a pet followed a similar pattern to those observed in Figure 6, however, the confidence intervals overlapped the null (Figure 7).

*Figure 7.* Temporal hazard risk in the 1-year excess major acute cardiovascular events in a) men and b) women, c) those living alone and d) those living with someone else in the home
Discussion

The main findings of the work of this thesis, based on the rich Swedish population and health registers with a unique linkage to registers of pet ownership and an extract from a large pet insurance company, are four-fold. Firstly, dog ownership in middle-aged and elderly Swedish men and women is associated with a lower risk of death from cardiovascular disease and death from all cause during follow-up. Secondly, we found that the risk of death was lower in dog-owners compared to non-owners after a first myocardial infarction or ischemic stroke. Thirdly, dog owners were not protected from hypertension or dyslipidaemia indicating that the lower mortality is likely not explained by these factors. Lastly, we found that owners are at increased risk of a MACE in the period after death of their pet, which has not been studied before.

A consistent finding was that individuals in single-occupancy households, as well as owners of dog-breeds previously bred for hunting, benefit the most from dog ownership. In contrast, ownership of mixed pedigree dogs was associated with an increased cardiovascular burden of health compared to non-dog owners even when controlling for education level and income.

Dog ownership and incident CVD and death

In Study I, a strong inverse association was found between owning a dog and the risk of composite CVD death and death from all causes. These findings were in contrast with two recent studies conducted on the subject. The Norwegian HUNT longitudinal study (n=28,746) found no association between dog ownership and mortality after adjusting for body mass index, physical activity levels and smoking. Similarly, in a study from the Health Survey of England (n=59,352), no association between dog ownership and CVD and all-cause mortality was detected across a lengthy follow-up period. However, the dissimilar findings are likely the results of methodological differences in both ascertainment of exposure and outcome as well as definitions of the study populations. These include differences in:

I Dog exposure – this was collected at baseline in both studies despite the long follow up times where dogs could have been dead, whilst this project had time-updated dog ownership including only periods where dogs were still registered to the owner.
Differences in the area of residence - in the HUNT study the population was a rural majority vs a nationwide coverage in this project.

Population included. - In this project, we excluded participants with previous CVD at baseline, whilst this was not part of the exclusion criteria for the previous studies.

Size – our study was by far the most well-powered on this topic.

With this study design, we were unable to investigate the mechanism underlying these observations. There are three main plausible explanations: Firstly, the CVD-free dog owners possibly achieve more regular physical activity than the non-dog owners, even in winter months when most would be unlikely to engage in outdoor activity.\(^{15,48}\) Regular physical activity is protective against the onset of, and/or progression of type 2 diabetes, as well as other diseases, and this further lowers the risk of morbidity and mortality from CVD and other diseases like cancer.\(^{43}\)

Secondly, dog ownership has been associated with psychosocial benefits. It is possible that some of the health benefits may have been mediated through a decrease in loneliness. Loneliness is an independent risk factor for premature death, having been associated with hypertension,\(^{105}\) coronary heart disease,\(^{106}\) and mortality;\(^{107}\) in our study, the gap in survival between singles and those living in multiple-person households were abolished when considering single dog owners only.

Thirdly, there may be unmeasured differences between dog owners and non-owner such as differences in health seeking behaviour, with dog owners seeking medical attention earlier as sickness would interfere with their normal dog walking activities – an earlier diagnosis would lead to earlier treatment and lower mortality. There could also be differences in personality among dog owners and non-owners contributing to a more healthy and social lifestyle. These factors acting together would decrease the risk of mortality quite significantly.

**Study I** also found a slightly lower risk of acute myocardial infarction in dog owners. We could not find a similar reduction in the stroke or composite CVD risks. According to both the INTERHEART\(^5\) and INTERSTROKE\(^6\) studies, the modifiable risk factors for CVD associated with myocardial infarction and stroke are similar. Thus, our findings of a reduction in myocardial infarction, but not ischemic stroke, may indicate a lower statistical power for the ischemic stroke outcomes. In addition, the lack of association for the composite-CVD outcome may indicate that the direction of association for one outcome may be in an opposite direction to another of the included outcomes resulting in a null result.
Dog ownership and cardiovascular risk factors

In **Study II**, we found a slightly higher risk of initiation of medication for hypertension and dyslipidaemia, in dog owners compared to non-owners. Although this was unexpected due to the lower risk of CVD death and death from all causes found in **Study I**, the results are similar to those found by Parslow et al, who showed that pet owners were more likely to present with higher diastolic blood pressures than non-pet owners. However, in our sensitivity analyses in TwinGene, we found evidence of the presence of additional confounders not captured in the national cohort analysis. We find it likely that the small increase in risk of hypertension and dyslipidaemia would have been abolished if we had adjusted for these factors, primarily employment status and non-CVD chronic disease status.

Moreover, a difference in health seeking behaviour between dog owners and non-owners may apply. It is possible that dog owners may be diagnosed earlier resulting in earlier treatment interventions and preventing cardiovascular events. As shown in the INTERHEART and INTERSTROKE studies, adequate treatment and control of hypertension and dyslipidaemia would significantly reduce the risk of death, and acute myocardial infarction. However, this does not account for the results found in the other CVD outcomes in **Study I**.

The observed similarity in risk of initiating treatment for both dyslipidaemia and hypertension in **Study II** may possibly be explained by increased surveillance for either condition when one or the other is diagnosed resulting in the observed concordance.

Although we could find no association of dog ownership with diabetes mellitus except in a few larger dog breeds, it is possible that some of the population received lifestyle interventions, such as dietary advice, that it was not possible to identify in the drug register.

Alcohol intake, physical activity and diet were not assessed in TwinGene. Due to the time span in between the SALT and TwinGene studies, we chose not to adjust for these factors in the analysis.

Dog ownership and death after CVD

In **Study III**, the risk of death from all causes was lower in dog owners than non-owners after either acute myocardial infarction or ischemic stroke. This is consistent with the findings by Friedmann et al, (n=369) who found that non-dog owners were 4 times more likely to die than dog owners after myocardial infarction independent of the severity of disease on admission. Pet ownership in that study was an independent predictor for survival.

In this project, the psychosocial support provided by the presence of the dog may have played a role in the better health outcome. A lack of social
support has been shown to influence mortality outcomes in human-human relationships. A randomized trial (n=48) also found that whilst medication alone could decrease the resting blood pressure in hypertensive patients, increased social support through pet ownership lowered blood pressure response to mental stress and thus improved overall outcomes.\textsuperscript{23} Whilst this may have explained some of our study findings, it did not account for it all.

It is furthermore possible that dog owners had better overall health with fewer comorbid conditions at the time of acute myocardial infarction or stroke. We could account for some measure of disease severity by adjusting for the Charlson comorbidity index, and this did not alter our findings. It cannot be excluded that dog owners may present to health facilities earlier than non-owners due to limitations that illness may pose to their dog walking activities.

The similarity in direction between the results of Study I and Study III provides confidence that similar underlying mechanisms are responsible for the association of dog ownership with lower mortality in the general population as in those that experience a myocardial infarction or stroke.

Pet loss and major acute cardiovascular events

To the best of our knowledge, Study IV represents the first study to explore cardiovascular health after the loss of a pet. Our novel results indicate that pet loss is associated with a time-dependent risk of MACE. In human-human relationships, excess cardiovascular mortality has previously been observed after the unexpected loss of a spouse.\textsuperscript{60} Both the severe emotional stress caused by the loss, and the sudden lack of social support, may play a role in provoking an immediate physiological stress reaction contributing to increased risk of death.

The results in this project suggest that pet loss may entail similar severe emotional stress and grief reactions as the loss of a person, and that pet bereavement may constitute an independent risk factor for CVD events. If these results are replicated, it means that both veterinary and health care professionals need to be aware of the potential health effects of pet bereavement, particularly, if a patient is in contact with health-care services during this time-period. Pet bereaved owners would require adequate support and not dismissal with comments like “it was just a dog”.

Another potential underlying mechanism, particularly in women, is reversible stress-induced cardiomyopathy.\textsuperscript{110} Approximately 2000 Swedish patients are diagnosed with this condition annually,\textsuperscript{111} and it has been associated with a 5.5% 28-day mortality.\textsuperscript{112} This condition can be precipitated by emotional stress presenting with symptoms that are difficult to distinguish from myocardial infarction. The underlying pathology is related to an increase in circulating catecholamines from both within the myocardium and the peripheral circulation.\textsuperscript{110} The resultant reaction is observable in both previously healthy and non-health individuals.\textsuperscript{113}
Mixed pedigree dogs
Ownership of mixed pedigree dogs was consistently associated with poorer outcomes in Study I, II and III. Mixed pedigree dogs are a heterogeneous group, with no defined breed and an unknown or complicated ancestry. Moreover, some “breeds” are not recognized by the Kennel Clubs and thus labelled as mixed breed e.g. “pitbulls”. These are more common in areas with lower socioeconomic resources. In a German survey (n=15,391), owners of mixed pedigree dogs were more likely to be first time dog owners, of younger age and of lower socioeconomic status. The finding of younger age and lower education and income was consistent with our study. They also reported more behavioural and health problems in their dogs than purebred dog owners. Dog breeders may selectively breed dogs that make better human companions, making the choice for purebred dogs more likely. Preference may also be given to breeds associated with lower known allergens, less aggressive behaviour or even less genetic disorders. Selectivity is easier in purebred than mixed bred groups.

To tease out the possibility of differences in owners, we adjusted for income, education level and latitude of residency, however, information on previous dog ownership, size of the dog, and behavioural problems in the dog that may discourage outdoor excursions was not available. We also would have liked to capture socioeconomic in more detail, adding information on unemployment, absence due to sickness and social class. These are variables available in the register, but were unfortunately not included in the linkage.

Unlike purebred dogs, which are almost all registered with the Swedish Kennel Club, it would be impossible to characterize the mixed breed group as it consists of a heterogeneous group of dogs. In order to characterize it correctly, all mixed breed dogs would have to be registered for character, size and breed-combination. This is logistically impossible and thus our study represents the best proxy of the national landscape.

Hunting breed dogs
Dogs originally bred for hunting, i.e. terriers, retrievers, pointing dogs, scent hounds and related dog, were associated with a lower risk of composite CVD and death from all causes (Study I); a lower risk of diabetes mellitus (Study II) and a lower risk of death after myocardial infarction and ischemic stroke (Study III). It is likely that dog owners perceive these breeds to have higher exercise needs than owners of other breeds, and this may provide an incentive for increased physical activity. In a Japanese survey (n=930), participants with higher levels of pet attachment were also more likely to achieve adequate levels of physical activity for both them and their dogs than non-dog walkers. In our population, it is possible that the overall health benefits were achieved via both physical activity and attachment.
In the smaller twin cohort, we found that dog owners reported higher levels of physical activity than non-owners, however, due to a smaller sample size, it was not possible to determine how this influenced disease outcomes in the hunting breed group owners.

Living alone
Dog owners who lived alone in the home had a lower risk of incident CVD and death from any cause (Study I) and a lower risk of death after acute myocardial infarction or ischemic stroke (Study III) compared to non-dog owners. Studies on weak social support and adverse health outcomes have shown that single living is associated with a higher risk of CVD.116 In two Scandinavian cohort studies (n=138,290117 and n=736116), living alone was associated with a higher risk of CVD and similarly, living alone is an independent risk factor for a poor prognosis after myocardial infarction.118 The reasons given for this include a lack of social support; engagement in risky behaviour including poor dietary habits, smoking and a decreased tendency to call for help in emergencies.117 In our study, the lower risk seen in those living alone may be due to a substitutive relationship (substituting human for animal companionship)73 by owners with their dogs that resulted in better health outcomes. Whilst the dog owners lived alone, it is possible that they were more physically active,119 had lower levels of social isolation and were thus less likely to experience stress, which is an independent risk factor for death after myocardial infarction.120

Methodological considerations
This doctoral project boasts the largest epidemiological study on dog ownership and cardiovascular risk to-date. The Swedish population registers provided a rich source of individual level longitudinally-collected data and has the great advantage of being updated regularly. The registers are largely complete with a low-level of loss to follow up.63 Some important limitations were however, taken into consideration:

Internal validity
To ensure that our results were internally valid, great efforts were made to account for bias and confounding. Some specific aspects included the following:
Selection bias

Selection bias is a distortion in a measure of association due to a sample selection that does not reflect the target population. In this project, one potential source of this bias was self-selection into dog ownership. The registers could not account for the possibility that the choice for ownership may be associated with non-random characteristics that differed between the exposed and the unexposed. Some of these characteristics may include heredity, an extroverted personality, or a prescribed change of lifestyle. We attempted to decrease the effect of these differences by adjusting for potential confounders. The question of self-selection into exposure would ideally be answered prior to acquiring a dog in a study that included the collection of information about motivation for dog ownership.

Another important type of selection bias is loss to follow up. The Swedish Register of the Total Population has the advantage of being able to account for emigration, death and immigration because it is updated annually. There is thus a very low level of loss-to-follow up.

The TwinGene sub-cohort of the Swedish Twin Registry may have suffered from a healthy volunteer bias and survivor bias. To be included in TwinGene, twins should have participated in the earlier SALT sub-study, consented to be followed up later and survived to the time of the next study, between 2 and 10 years later. Of the 22,390 invited twins only 12,614 (56%) participated. The majority of responders were recent pensioners (born between 1936-1940), and more likely to be healthy as they needed to be able to attend physical and clinical examinations at local health centers. The strength of including this population in Study II was that there was a wealth of personal characteristics and clinical variables available to adjust for and strengthen the case for the observed associations in the national cohort.

Information bias

Information bias refers to a bias that arises from measurement error, this could be either in an error in measurement or misclassifying the observation for exposure or outcome. The exposure, dog ownership, may have been misclassified in Study I, II and III. We attempted to minimize this bias by including partners’ dog registration as ‘exposed to dog ownership’, but in situations where two people were cohabiting without children in common, dog ownership may have been missed in one of the partners. We may also have underestimated the proportion of dog ownership in the Twin cohorts as partners’ information was not available. This was not the case in Study IV where all participants were identified by their pet ownership status. Furthermore, the Swedish Board of Agriculture register increased its coverage during the time-period, but restricting the analysis to different periods did not affect the results.
The exposure pet bereavement was based on veterinary reports to the insurance company, usually based on copies of the medical records or autopsy reports. There may have been some misclassification on the exact dates of pet death that would affect the classification of the events during the first few weeks after death, but this would be a random error.

For the outcomes in Study II, initiation of treatment for diabetes mellitus may have been misclassified. Type 2 diabetes may have a delayed diagnosis, or when diagnosed early, patients may be prescribed lifestyle changes before the administration of medication. The Swedish Prescribed Drug Register does not gather such information. This misclassification would have attenuated the observed associations.

Cardiovascular outcomes in the National Patient Register could have been misclassified. However, to ensure consistency, we only included those diagnoses recorded as the primary diagnosis, and based on validity studies conducted on this register, we were confident about the high diagnostic and reporting validity.

Outcomes in the Cause of Death Register have a high level of validity and are largely complete. In 2015, only 0.9% had a missing diagnosis in the death register.

Confounders

In general, cohort studies use covariates measured at baseline and assume that the variables remain static through the study period. The Swedish population registers allowed us to have time-updated measures on variables including marital status, home occupancy, income, population density and area of residence. This helped us to adjust for changes happening during the study period. Although we had access to information on several variables, we could not account for lifestyle related factors such as tobacco use and physical activity in the national cohort and had to restrict their use to the smaller twin cohort.

Residual confounding

Residual confounding results from the absence of important causally related covariates in a model resulting in spurious associations between the exposure and outcome. Whilst this is always a liability with observational data where no randomization is performed on the exposure of interest, our access to a multitude of both register-based and survey-based covariates helped to minimize the risk of residual confounding. Better capture of information on physical activity, socioeconomy and availability of information on diet and tobacco use would have been useful.
Reverse causation
Reverse causation occurs when it is difficult to establish the temporal sequence of events in an observational study. Although we had excluded those with previous-CVD in Study I and Study II, we could not exclude the possibility that study participants were less likely to own dogs due to disabilities or other comorbidities, and were already at higher risk of CVD or mortality. We tried to determine extent of this effect using the smaller Swedish Twin Registry population, but could not exclude the possibility of some bias remaining in the observed associations.

Missing data
Missing data in epidemiological studies poses a risk to making wrong deductions from the observed associations. In this project, information on the level of education was only complete for those aged 75 years and below, based on administrative procedures done annually by Statistics Sweden. However, based on recommendations from research by Winkleby et al., that looked at socioeconomic status and cardiovascular health, we used age-adjusted income as a proxy for socioeconomic status and conducted sensitivity analyses that additionally adjusted for education in complete-case analyses. The results did not differ from those where only age-standardized income was used as illustrated in Study I, II and III.

External validity
External validity refers to how well the results from our study can be generalized to and across individuals, settings and times. By making use of a large population size, the rich registers and applying robust study designs, it has been ensured that these results can be generalized to similar westernized populations with similar regulations for dog ownership.
Conclusion

This thesis provides some evidence of a positive impact of dog ownership on cardiovascular health, while further also identifying potential deleterious health effects of losing such a canine relationship.
Future Perspectives

“When the Man waked up he said, ‘What is Wild Dog doing here?’ And the Woman said, ‘His name is not Wild Dog any more, but the First Friend, because he will be our friend for always and always and always.’”

Rudyard Kipling (The Jungle Book)

Whilst this project provides exciting reasons to advocate for dog ownership, some important aspects need further investigation. Firstly, the underlying motivation for self-selection into dog ownership needs to be investigated. Understanding key aspects of the dog owner such as personality type, enjoyment of physical activity and perhaps heredity, need to be addressed in well-designed studies. This could be done by establishing registers to collect detailed information on new dog owners prior to ownership. These registers would also collect information on the choice of dog breed.

Secondly, physical activity needs to be measured by the use of devices such as accelerometers on both the dog and owner to move away from reliance on owner memory and recall bias. This would provide some insight into the direct association between dog ownership and physical activity, and the role the dog breed has on level of physical activity in the owner.

Thirdly, studies that can establish temporality need to be undertaken. The association between dog ownership and cardiovascular risk factors such as hypertension, dyslipidaemia and diabetes mellitus needs to be examined further. In our study, the question arose as to whether initiation of medication for hypertension and dyslipidaemia was associated with better health seeking behaviour. This may arise from an earlier recognition of symptoms due to difficulties when owners are walking their dog.

Finally, we were unable to establish the reason why dog ownership was associated with lower CVD and all-cause death. Studies that investigate the potential differences in the microbiome of dog owners from non-dog owners, and how these potential changes may be related to lower inflammation and heart disease would be interesting. With the current advances in One Health, the importance of studying the different relationships that underlie the interactions between humans and animals are important.126,127

Den första studien beskriver sambandet mellan hundägande och hjärt sjukdom och död. Av de 3 432 153 personer som ingår var hundägande (13,1%) förknippat med en lägre risk för dödsfall på grund av hjärtsjukdom och dödsfall med 23% respektive 20%. Dessa fördelaktiga effekter var mer uttalade där ägande var av raser från grupperna terrier, stötande hundar, apporterande hundar och vattenhundar, drivande hundar samt sök- och spårhundar och stående fågelhundar - hundar som ursprungligen föddes för jakt. För personer som bodde ensam med en hund var risken för att få en hjärtsjukdom lägre än för de som bodde ensamma utan hund. Vidare var risksänkningen för dödsfall mer påtaglig än när personer i flerpersonshushåll med och utan hund jämfördes med varandra. När vi undersökte hur resultaten påverkades när vi använde en mindre men mer välbeskriven tvillingpopulation fann vi att tillägg av livsstilsfaktorearna bibehöll liknande resultat som de i det nationella registret.

Den andra studien beskriver sambandet mellan hundägande och risken att påbörja behandling för högt blodtryck, onormala blodfetter eller diabetes hos 2 026 865 vuxna. Hundägande (14,6%) var förknippat med en något högre risk för att behandlingen startades (2%) för högt blodtryck och onormala lipider, men inte för diabetes mellitus. Det krävs dock mer forskning om detta eftersom vi inte kunde ta hänsyn till viktiga faktorer som kronisk sjukdom och arbetslöshet, som i den tidigare nämna tvillingpopulationen verkade ha betydelse för sambanden.
Den tredje studien beskriver risken för dödsfall efter en akut hjärtinfarkt eller stroke. Hundägande var förknippat med en 20% -24% lägre risk för dödsfall under uppföljningstiden. I de tre första studierna sågs generellt en bättre hjärtkärlhälsa hos ägarna till de tidigare nämnda jaktrasgrupperna, medan ägare till hundar av blandad stamstam hade en sämre hjärthälsa.

I den fjärde studien studerades risken för hjärtkärlsjukdom tiden efter ett dödsfall av ett livförsäkrad hund eller katt. Risken befanns vara förhöjd.

Avhandlingen har utnyttjat de svenska befolknings- och hälsoregistrerna för att undersöka förhållandet mellan olika aspekter av hundägande och hjärt-risk. Genom att använda definierade mätbara slutpunkter och statistiska metoder har detta projekt gjort ett betydande bidrag till den forskning som ser på förhållandet mellan hundägande och människors hjärtkärlhälsa. Även om sambanden är tydliga, kan några klara besked om orsak-verkan dock inte ges med den här typen av studier, då det kan finnas yttre faktorer som påverkar både risken för sjukdom och hundägande.
There is a proverb that echoes throughout the land of my birth – “it takes a village to raise a child.....” The journey to the fruition of this published work stands as a testament to the tireless efforts of so many. I would like to take this opportunity to express my gratitude to:

My Main Supervisor Tove Fall, your enthusiasm for this work, unfailing assistance and encouragement have been an incredible lesson in leadership. Thank you for allowing me to learn from your passionate pursuit of excellence and a relentless quest for answers. Your guidance through the mountain of data was no small feat - thank you so much for your patience and friendship.

My co-supervisor Liisa Byberg, thank you so much for making epidemiology and statistics seem so easy. You have been a huge support in my quest for knowledge and for that I am truly grateful. Additional thanks for all the delightful academic and non-academic discussions.

My co-supervisor Erik Ingelsson, I am sincerely thankful for your availability despite your busy schedule. Thank you for your scientific skepticism, guidance and for being a role model even from a distance.

Agneta Egenvall, for your engagement and attention to detail. You have consistently provided wonderful insights as the project has unfolded.

Patrick Magnusson, Fang Fang and Johan Sundström for allowing me to learn from you, and for your patience with the co-authored work.

Pontus Freyhult, for technical assistance whilst I worked on the Mosler servers. Thank you for the quick responses and always providing solutions.

Christian Berne, for the embodiment of what a great scientist should be. For insights in research, policy and life that have made the Monday meetings so fulfilling.

Julie Phillips, a native mentor in a foreign land. For the clarity, perspective and encouragement. You brand of leadership constantly amazes and delights me.
I would like to commend each member of the Tove Fall Research group - for your tireless, unbounded scientific contribution to my growth. ‘it is said to go fast, walk alone, to go far, walk together,’ - thank you all for helping to get me this far. Emily for your assistance, warmth and time; Markus for every scientific and non-scientific discussion, and allowing me to use you as a sounding board more times than I could possibly count; Mona-Lisa for friendship and the enjoyable SINGS trips together, but most especially for the sacrifice in a wonderful tour of Gothenburg; Samira for every heartfelt discussions and your encouragement; Stephan for your calming disposition and your assistance over the years (and for making my coca-cola habit look cool); Ulf for reading and constructively criticizing the very rough drafts of my work; Shafqat for your own work which I referred to as I prepared my manuscript and to Beatrice, my gratitude to you is without limit - thank you for allowing me to be random and for your fast friendship, but more than that, for rescuing me many times over.

To the Zebra Fish Group – Marcel, Bene, Manoj, Anastasia, Ci, Tiffany, David, Chrissy and the whole team, I am grateful for the many hours of scientific and social engagement.

Karl Michaëlsson, Carl Brunius, Marianne, Anna-Karin, Erika, Eva, Jonas, Adam, Karl S, Elise, Kia and all my incredible colleagues at Epihubben, for fostering an environment in which to scientifically grow and thrive; for all the wonderful discussions and for making the last few months of my program thoroughly enjoyable.

To the Molecular Epidemiology Group Alumni – Casimiro, Naomi, Susane, Chris, DanieLA, Jittendar, Andrea, Dan and Sari. Thank you for the Science, the brilliance to aspire to and for always allowing me to call on you despite your change in location.

Johan Dixelius, Gustaf Floderus, Linda Dunder, Rolf Larsson and Karin Eriksson – serving with you on the Equal Opportunities Committee was a great honour. Thank you for the privilege.

The Department of Medical Science at Uppsala University for providing the infrastructure and environment to nurture my scientific growth. Particular thanks go to Katarina J. Vangen, Gabriella Widerberg and Susanne Westholm for your patient indulgence of my endless administrative questions; and to Anna Foyer, my miracle worker, for your open door, smiles and always allowing me to leave your office with more than I bargained for.
I am grateful for the funding from the Agria Research Foundation and the Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning that made this project possible.

I also wish to thank the The Swedish Twin Register, the Swedish Kennel Club, the Swedish Board of Agriculture and the Agria Insurance Company for access to data and indulging my repeated requests for clarity. Particular thanks are extended to Barbro Sandin for your assistance with my navigation through the Twin Registers.

Anita Berglund, and the incredible team at the Swedish Interdisciplinary Graduate School, for all your assistance in helping me to develop a deeper understanding of the science of registers. Thank you for the methodology and epidemiology lessons; for the trips around the country, but most of all, for an interdisciplinary environment that has fostered life-long professional relationships.

My sincere gratitude is also extended for the many opportunities I was afforded to present this project, learn new methods and work with others both locally and abroad. The funding for this was made possible by the generous support from Uppsala University, the Hjärt-Lungfonden, the World Heart Federation, the Mayosi Group Scholarship and the One Health Platform.

The late Professor Bongani Mayosi who demonstrated excellence in everything he did; taking a chance on a lost medic and teaching me how to provide answers to the needs of my community through research.

Rudzani Muloiwa, Jan Kunene, Sula Mazimba and Fastone Goma, the geniuses who have played vuvuzelas for me even at my lowest; for always reminding me that the race is not to the swift……thank you.

My utmost thanks to those whose contributions were not directly related to this project, but who oiled the other parts of my life and helped make its completion possible. In Sweden, Carin Backlin, Sheila, Frederick, Sharon, Jeff, Clive, Ropafadzo, Maria, Ruby, Mukuka, Nanda, the Obengs, Mensas and Marbuahs for opening your minds, hearts and homes to me. For being my family in a place far from home and helping me enjoy the journey more. Around the World, Babalwa, Cynthia, Tewaa, Thando, Tabeth, Agnes, Monica, Faith, Judy, Bridget and Luse - your calls, visits, assistance and your friendship over the years has meant so much. Ma Lilian Chimukupete, for adopting and celebrating me, and then forcing me to stand on stages I never dreamed possible. Thank you for all the memorable adventures.
Finally, to my tribe, my precious family, for love and sacrifice above and beyond the call of duty, when all is said and done, I owe this all to you.
To my grandfathers who both taught me that the only limits that were insurmountable were the ones in my mind. Mum Diane for the daily phone calls that allowed me to vent and feel close to home from so far away.
Dad and Mum, my heroes, role models and the embodiment of ‘love-in-a-body’, thank you so much for always cheering me on, supporting and praying for me, and for encouraging me to spread my wings.
Tisa, Lombe, Kalo, Bwalya, Janet and Bupe, our lives have been an incredible journey; thank you for every adventure, the chats that have kept me sane and for always having my back. Manny, Nate, Asher and Michelle to the babies who make it all worth it.
And to William, thank you.

“Mulelondolola ubulumbwa bwa bulamba bwakwa Yawe mwe ndupwa shamishobo, mulelondolola ubulumbwa bwa bucindami bwakwa Yawe na maka yakwe. Mulelondolola ubulumbwa ubwalinga ishina lyakwa Yawe, muleleta no mutuulo pakwisa pa cinso cakwe. Mulepepa Yawe mu bucindami bwamushilo wakwe”
References


80 Ludvigsson, J. F., Otterblad-Olausson, P., Pettersson, B. U. & Ekbom, A. The Swedish personal identity number: possibilities and pitfalls in healthcare and


Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1490

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)