

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Dog ownership and Cardiovascular Risk Factors: a nationwide prospective register-based cohort study
AUTHORS	Mubanga, Mwenya; Byberg, Liisa; Egenvall, Agneta; Sundström, Johan; Magnusson, Patrik; Ingelsson, Erik; Fall, Tove

VERSION 1 – REVIEW

REVIEWER	Dr Carri Westgarth and Rebecca Purewal Institution of Infection and Global Health University of Liverpool, UK
REVIEW RETURNED	08-May-2018

GENERAL COMMENTS	<p>This is an interesting paper exploring the association between dog ownership and cardiovascular risk factors. Please find review comments below.</p> <p>Abstract The abstract appropriately highlights the important findings of the study. However in line 16 (pg 2), authors state they adjusted for socioeconomic status but later in the discussion section they mention that not controlling for SES data is a limitation. Therefore, to be clear in the abstract authors should be specific on what SES variables they controlled for e.g. education, area of residence etc. The next sentence in Line 16 (pg 2) 'Participants were followed up to medication for a cardiovascular risk factor, emigration, death or at the end of the study on December 31st, 2012' is unclear. Change to 'Participants were followed up to the end of the study on December 31st, 2012 assessing medication for a cardiovascular risk factor, emigration and death. Line 19 (pg 2) does not explain what or which risk factors from TwinGene were assessed in cross-sectional associations Line 31 (pg 2) (results) should include 'After adjustment for...(insert confounders)' at the start of the sentence before stating the results. Line 37 (pg 2) - 'Sensitivity analyses in the TwinGene cohort indicated confounding...' confounding of what? Dog ownership?</p> <p>Introduction The introduction is well-written, and succinctly summarizes previous research related to dog ownership and cardiovascular health. However it is very short; if the word count allows, it could be expanded. Citations need to be added as stated below: Line 10 (pg 4) - 'Any causal association of dog ownership with lower cardiovascular mortality...' sentence needs to be expanded with citations to support these hypotheses.</p>
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	<p>Line 17 (pg 4) 'An alternative explanation...' again needs to be expanded with citations to show socioeconomic/demographic associations with dog ownership</p> <p>Line 35 (pg 4) - aim needs a citation to show that these are clinical risk factors for CVD</p> <p>The authors could further demonstrate the need for investigations in the topic area e.g. how and why would this benefit the population?</p> <p>Gaps/limitations in the current research are appropriately highlighted. It could be made clearer for the reader that the authors aim to address these limitations (low statistical power in small studies, use of restricted or homogenous populations, inability to control for differences across breed of dogs) in the present study to establish originality of the research aims.</p> <p>Materials and Methods</p> <p>Line 19 (pg 5) - 'We excluded 11,298 individuals with unverified, re-used identification numbers or missing education information, and 137,306 additional individuals that had resided in Sweden for <15 years to ensure complete linkage to medical information and sufficient information regarding dog ownership in Sweden.'</p> <p>Change structure to- 'To ensure complete linkage to medical information and sufficient information regarding dog ownership in Sweden, we excluded 11,298 individuals with unverified, re-used identification numbers or missing education information, and 137,306 additional individuals that had resided in Sweden for <15 years.'</p> <p>Line 24 (pg 5) - 'We also excluded 531,658 individuals with a history of any CVD (International Classification of Disease (ICD) -9 codes 390-459 and ICD-10 I00-I99) or with a history of coronary artery bypass grafts or percutaneous coronary artery intervention medical procedure (Nordic surgical procedure codes FNA, FNC and FNG) from in- and outpatient data from the National Patient Register before October 1st, 2006.' Change structure to 'We also excluded 531,658 individuals with a history of any CVD (International Classification of Disease (ICD) -9 codes 390-459 and ICD-10 I00-I99) before October 1st, 2006, or with a history of coronary artery bypass grafts or percutaneous coronary artery intervention medical procedure (Nordic surgical procedure codes FNA, FNC and FNG) from in- and outpatient data.'</p> <p>Line 7 (pg6)- change sentence structure to- The TwinGene study originally included 12,614 (of 22,391 invited) twins from the "Screening Across the Lifespan Twin study" (SALT), was conducted between April 2004 and December 2008 and included a visit to their local health center and blood sampling (Supplementary Figure 2).</p> <p>Line 32 (pg 6)- How can we distinguish if partners were living together, and therefore who lived with the dog?</p> <p>Line 48 (pg 6)- 'If information on a dog's death was missing, we assumed a maximum lifespan of ten years.' Is this realistic? Any evidence to support this? How do the authors know that information was updated on dog's death?</p> <p>Line 7 (pg 7)- needs a citation</p> <p>Line 15 (pg7)- What if participants' health condition was not being treated by drugs? Could this be a limitation?</p> <p>Line 40 (pg 7) 'hsCRP and triglycerides were transformed to the natural log scale before analysis to approach normality' Needs to be moved to the Statistical analyses section below.</p>
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	<p>Line 30 (pg 8)- change sentence structure to 'In addition to adjusting for age, sex, presence of children in the household, area of residence, population density, marital status, latitude of residence and level of education, we added further covariates, one at a time to investigate their individual importance: tobacco use, occupational level, employment status, Charlson comorbidity index and disability.'</p> <p>Some general thoughts on the analysis - What about physical activity as a covariate? What physical activity is attributable to dog ownership, and what physical activity is done without a dog? Is physical activity available in TwinGene?</p> <p>It is common for dog owners not to walk their dogs (especially if they suffer from chronic physical health disorders). Was any data available to explore if and how often people walked their pets, and if this related to CVD and/or initiation of treatment?</p> <p>Besides initiation of treatment for CVD, any measure of medicines adherence? It could be interesting to examine differences between dog and non-dog owners according to long-term adherence</p> <p>The original Swedish study that found dog owners at lower risk of CVD looked at patients aged 40-80; could this have implications looking at slightly different age groups? Especially considering CVD is more common in people over 50, the risk of developing it increases throughout age.</p> <p>Looking at the main outcomes, hypertension, dyslipidaemia and diabetes mellitus, were these stratified appropriately? People with diabetes are more likely to suffer from all three conditions, was this controlled for?</p> <p>3. Results and Discussion</p> <p>On the whole, information from results, discussion and data tables is clear, and trends support the conclusions.</p> <p>Line 27 (pg 9)- 'During 10,692,258 person-years of follow-up, dog ownership was associated with a 2% higher risk of initiation of anti-hypertensive drug medication in both crude and multivariable adjusted analyses..' Dog ownership when? At any time? Over a long time period? Was a minimal time period set? As someone may have been only a brief time owning a dog? How dog ownership was measured and structured in analysis needs to be clearer in methods and presentation of results.</p> <p>Line 7 (pg 11)- We know that owners of companion/toy breeds are likely to walk dog less and therefore have a lower overall physical activity. This is mentioned in line 49 'The level of dog walking might be lower in the smaller companion/toy dogs breeds as compared to the hunting-type breeds.¹⁹ In TwinGene, 68% of hunting breed owners reporting a high level of physical activity versus 52% in non-dog owners.' This sentence needs moving up two paragraphs to line 7. Have authors thought about doing a mediation analysis or controlling for physical activity? What happens to the dog ownership variable subsequently?</p> <p>Line 26 (pg 12)- the possible misclassification of dog ownership was also present in the main study; is this not a great potential limitation? Further limitations include no information on dog walking, physical activity levels or dog attachment. Studies have shown these factors are likely to be important mediators between dog ownership and health outcomes. Other limitations (I think) include not fully accounting for the time or length of dog ownership. It is also not clear whether the dog ownership data is particularly reliable in the main study. For example how good are people at notifying that their dog has died?</p>
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	<p>The unavailable information on comorbidity, disability and body mass index is a major flaw (national cohort) and could be mentioned again in the limitations section.</p> <p>Authors could attempt to explain/mention other potential mechanisms of the pet effect e.g. increased social well-being, decreased psychological stress, and immune system development, as additional reasons why dog ownership could offer protection against cardiovascular disease and death.</p> <p>Table 1 Line 12 (pg 16) - Dog owners here are individuals who had a registered dog at any time point during the study period; however this may not be a time period close to when individuals have a health condition, nor for very long? This leads me to the questions I have raised regarding dog ownership measurement and potential limitations that are currently not clear.</p> <p>Supplementary Table 1 Line 4 (pg 27)- Edit large space in variable created column in regards to exercise</p> <p>Supplementary Table 3 Line 8 (pg 29)- 'XX' needs defining</p> <p>Supplementary Table 5 Line 9 (pg 30)- 'dog ownership status on the date of clinical examination and other non-clinical details extracted from the SALT questionnaire (1998-2002)'- I am a little confused as to the time point of dog ownership measurement and whether this is concurrent with when exercise was measured</p> <p>Supplementary Figure 3 Not easy to interpret and therefore does not really add value, is there a clearer way of portraying this?</p>
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REVIEWER	Erika Friedmann University of Maryland
REVIEW RETURNED	22-Jun-2018

GENERAL COMMENTS	<p>The paper presents an interesting analysis of an excellent data source, a national health registry that can be linked to files that include pet ownership. The longitudinal nature of the data and the use of the twin data enhance the value and complexity of the analysis. I am concerned about the use of so many predictors as confounders/covariates in the analysis in the sense that many of them may be related not only to the outcome but also to likelihood of pet ownership. For example employment status, income, area of residence, marital status, presence of children in the household all may be predictors of dog ownership. Thus the study suffers from the problems typical of cohort studies being used to evaluate the effects of "interventions" that were not part of the study design. Propensity analysis or marginal structural models are modern modeling techniques that would enhance the approach to enable better evaluation of the actual impact of pet ownership as a "intervention" to reduce incidence of medication.</p> <p>In addition, the authors did not discuss (based on other studies of the health effects of pet ownership) the possible basis for the differences in the results of their previous analysis, showing that mortality was decreased with dog ownership, and the results of</p>
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	<p>this set of analyses with respect to what they might mean about the influence of pet ownership on health. It is also not clear why they authors were interested in specific breeds of dogs - even 10 groups seems excessive. The basis for grouping the dog breeds also is unclear. A minor issue</p> <p>Supplementary table 3 - "XX" in title should be replaced with a year.</p> <p>It could be helpful to readers to have complete analyses, with all covariates, included as supplementary tables.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Dr Carri Westgarth and Rebecca Purewal

Institution and Country: Institution of Infection and Global Health,
University of Liverpool, UK

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This is an interesting paper exploring the association between dog ownership and cardiovascular risk factors. Please find review comments below.

Abstract

1. Reviewer comment: The abstract appropriately highlights the important findings of the study. However in line 16 (page 2), authors state they adjusted for socioeconomic status but later in the discussion section they mention that not controlling for SES data is a limitation. Therefore, to be clear in the abstract authors should be specific on what SES variables they controlled for e.g. education, area of residence etc.

Authors' reply: The authors would like to acknowledge the insightful comments and detailed review that helped to improve the manuscript. We have now specified the adjustment for education level and income. To be able to incorporate this and the other excellent suggestions for the abstract within the word limit, we have slightly rewritten the abstract and we hope that it now reads more clearly.

2. Reviewer comment: The next sentence in Line 16 (page 2) 'Participants were followed up to medication for a cardiovascular risk factor, emigration, death or at the end of the study on December 31st, 2012' is unclear. Change to 'Participants were followed up to the end of the study on December 31st, 2012 assessing medication for a cardiovascular risk factor, emigration and death.

Authors' reply: Thank you, we have made the appropriate changes on page 2.

3. Reviewer comment: Line 19 (page 2) does not explain what or which risk factors from TwinGene were assessed in cross-sectional associations

Authors' reply: Thank you, we have now added this information to the Methods part of the Abstract as stated below on page 2:

New text (page 2): Cross-sectional associations were further assessed in 10,110 individuals from the TwinGene study with additional adjustment for professional level, employment status, Charlson comorbidity index, disability and tobacco use.

4. Reviewer comment: Line 31 (page 2) (results) should include 'After adjustment for...(insert confounders)' at the start of the sentence before stating the results.

Authors' reply: We agree with the Reviewers that this would be an important addition. However, due to restrictions with the word limit for the abstract, we are unable to specify all confounders in the abstract.

5. Reviewer comment: Line 37 (page 2) - 'Sensitivity analyses in the TwinGene cohort indicated confounding...' confounding of what? Dog ownership?

Authors' reply: We apologize for being unclear, we have now rewritten the specified sentence as stated below on page 2:

New text (page 2): Sensitivity analyses in the TwinGene cohort indicated confounding of the association between dog ownership and prevalent treatment for hypertension, dyslipidemia and diabetes mellitus, respectively, from factors not available in the national cohort, such as employment status and non-CVD chronic disease status.

Introduction

6. Reviewer comment: The introduction is well-written, and succinctly summarizes previous research related to dog ownership and cardiovascular health. However it is very short; if the word count allows, it could be expanded. Citations need to be added as stated below: Line 10 (page 4) - 'Any causal association of dog ownership with lower cardiovascular mortality...' sentence needs to be expanded with citations to support these hypotheses.

Authors' reply: We have added suitable references, as seen below on page 4:

New text (page 4): Any causal association of dog ownership with lower cardiovascular mortality could potentially be mediated through increased physical activity[1, 2] or through the psychological benefits of companionship,[3] which could in turn reduce other important cardiovascular risk factors such as blood pressure, adiposity, dyslipidemia, and insulin resistance.[4, 5]

7. Reviewer comment: Line 17 (page 4) 'An alternative explanation...' again needs to be expanded with citations to show socioeconomic/demographic associations with dog ownership

Authors' reply: Thank you the appropriate changes have now been made , as seen below:

New text (page 4): An alternative explanation could be confounding by socioeconomic, [6] cultural,[7] demographic[6] or psycho-social factors.[8, 9]

8. Reviewer comment: Line 35 (page 4) - aim needs a citation to show that these are clinical risk factors for CVD The authors could further demonstrate the need for investigations in the topic area e.g. how and why would this benefit the population?

Authors' reply: Thank you. A citation to the clinical risk factors has now been added on page 4.

New text (page 4): The aim of this study was to assess the association of dog ownership with three major clinical risk factors for cardiovascular disease,[10] specifically hypertension, dyslipidemia and

diabetes mellitus. We hypothesized that the cardiovascular risk profile of dog owners is better than that of non-dog owners.

9. Reviewer comments: Gaps/limitations in the current research are appropriately highlighted. It could be made clearer for the reader that the authors aim to address these limitations (low statistical power in small studies, use of restricted or homogenous populations, inability to control for differences across breed of dogs) in the present study to establish originality of the research aims.

Authors' reply: Thank you; we have now added the following statement on page 4:

New text (page 4): To overcome the limitations of previous studies concerning study size, generalizability and differences between dog breeds, we investigated this hypothesis using data on all Swedish residents aged 45-80 years of age in 2006 from national registers on dog ownership and drug prescriptions.

Materials and Methods

10. Reviewer comment: Line 19 (page 5) - 'We excluded 11,298 individuals with unverified, re-used identification numbers or missing education information, and 137,306 additional individuals that had resided in Sweden for <15 years to ensure complete linkage to medical information and sufficient information regarding dog ownership in Sweden.' Change structure to- 'To ensure complete linkage to medical information and sufficient information regarding dog ownership in Sweden, we excluded 11,298 individuals with unverified, re-used identification numbers or missing education information, and 137,306 additional individuals that had resided in Sweden for <15 years.'

Authors' reply: Thank you, we have made the appropriate changes on page 5.

11. Reviewer comment: Line 24 (page 5) – 'We also excluded 531,658 individuals with a history of any CVD (International Classification of Disease (ICD) -9 codes 390-459 and ICD-10 I00-I99) or with a history of coronary artery bypass grafts or percutaneous coronary artery intervention medical procedure (Nordic surgical procedure codes FNA, FNC and FNG) from in- and outpatient data from the National Patient Register before October 1st, 2006.' Change structure to 'We also excluded 531,658 individuals with a history of any CVD (International Classification of Disease (ICD) -9 codes 390-459 and ICD-10 I00-I99) before October 1st, 2006, or with a history of coronary artery bypass grafts or percutaneous coronary artery intervention medical procedure (Nordic surgical procedure codes FNA, FNC and FNG) from in- and outpatient data.'

Authors' reply: Thank you, we have made the appropriate changes on page 5.

12. Reviewer comment: Line 7 (pg6)- change sentence structure to- The TwinGene study originally included 12,614 (of 22,391 invited) twins from the "Screening Across the Lifespan Twin study" (SALT), was conducted between April 2004 and December 2008 and included a visit to their local health center and blood sampling (Supplementary Figure 2)

Authors' reply: Thank you, we have now made the appropriate changes on page 6.

13. Reviewer comment: Line 32 (page 6) - How can we distinguish if partners were living together, and therefore who lived with the dog?

Authors' reply: Thank you for asking for clarification. We have changed the sentence to provide more clarity:

New text (page 6): The identification of partners was possible through annual extracts from the Register of the Total Population that keeps track of couples that are married, registered in same-sex partnership or are cohabiting with common children.

14. Reviewer comment: Line 48 (page 6)- 'If information on a dog's death was missing, we assumed a maximum lifespan of ten years.' Is this realistic? Any evidence to support this? How do the authors know that information was updated on dog's death?

Authors' reply: There was information on dog death available in the Swedish Kennel Club dog register but this information was not complete 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.[11]

In this study, we had 295,682 registered dog owners. From these, dog ownership was changed to a different owner in 5,822 (2.0%) dogs and 14,803 (5.0%) dogs were recorded as having a dog that died during the study period. In addition, 174,167 (58.9%) dogs were born between the start of the study on 1st October 2006 and the end of the study on 31st December 2012. Please, also see our answer to your comment #29 (below), where we have conducted sensitivity analysis censoring dogs at age 8 and 12 instead.

15. Reviewer comment: Line 7 (page 7)- needs a citation

Authors' reply: Thank you, we have added the reference so that the statement now reads:

New text (page 7): Based on previous findings of owners to hunting dogs having a lower risk of cardiovascular events,[12] we additionally defined a group of hunting dogs consisting of Terriers, Pointing, Scent Hounds and Retrievers for analysis.

16. Reviewer comment: Line 15 (pg7)- What if participants' health condition was not being treated by drugs? Could this be a limitation?

Authors' reply: Thank you, we agree and apologize for not mentioning this previously. This limitation has now been added to the discussion.

New text (page 14): Another important limitation is that we were unable to account for those that did not initiate treatment due to any of the three conditions. The Prescribed Drug Register does not keep a record of adherence to treatment or records of those prescribed lifestyle interventions such as diet or exercise.

17. Reviewer comment: Line 40 (page 7) 'hsCRP and triglycerides were transformed to the natural log scale before analysis to approach normality' Needs to be moved to the Statistical analyses section below.

Authors' reply: We have made the appropriate changes on page 8.

18. Reviewer comment: Line 30 (page 8)- change sentence structure to 'In addition to adjusting for age, sex, presence of children in the household, area of residence, population density, marital status, latitude of residence and level of education, we added further covariates, one at a time to investigate their individual importance: tobacco use, occupational level, employment status, Charlson comorbidity index and disability.'

Authors' reply: We have made the appropriate changes on page 8.

19. Reviewer comment: Some general thoughts on the analysis - What about physical activity as a covariate? What physical activity is attributable to dog ownership, and what physical activity is done without a dog? Is physical activity available in TwinGene?

Authors' reply: Information on exercise was available in the original SALT study from which the TwinGene sub-study was derived. It was not included in the TwinGene questionnaire. However, we decided against using it because the information was between 2 to 10 years old at TwinGene study baseline was conducted and we could not account for changes in lifestyle during the period between the two studies. In addition, we also believe that unless specifically requested on a questionnaire, it is difficult to extrapolate what physical activity is performed with or without the dog, making adjustment for physical activity a challenge. We have added the following sentence to the discussion:

New text (page 13): At the same time, while national registers allow for large and unselected populations with no loss to follow-up, they lack information on individual attributes such body mass index, blood pressure, lipid levels and physical activity.

20. Reviewer comment: It is common for dog owners not to walk their dogs (especially if they suffer from chronic physical health disorders). Was any data available to explore if and how often people walked their pets, and if this related to CVD and/or initiation of treatment?

Authors' reply: Unfortunately, we do not have this information. However, we adjusted for the Charlson comorbidity index and disability to account for frailty on initiation of treatment in TwinGene. The information available on exercise was unfortunately, not tied to dog ownership. Dog ownership was determined from non-questionnaire based administrative registers, and thus we had significant limitations on making assumptions about who had responsibility for walking the dog.

21. Reviewer comment: Besides initiation of treatment for CVD, any measure of medicines adherence? It could be interesting to examine differences between dog and non-dog owners according to long-term adherence

Authors' reply: This is indeed an interesting consideration. Unfortunately, the Prescribed Drug Register only has information on the drugs dispensed and not on whether the patients adhere to treatment or not. Assumptions can only be made based on regularity of refills and in this study; we only examined the association with initiation of treatment. However, there is no evidence from the literature that dog owners and non-owners have differences in adherence.

New Text (page 13): Another important limitation is that we were unable to account for those that did not initiate treatment due to any of the three conditions. The Prescribed Drug Register does not keep a record of adherence to treatment or records of those prescribed lifestyle interventions such as diet or exercise.

22. Reviewer comment: The original Swedish study that found dog owners at lower risk of CVD looked at patients aged 40-80; could this have implications looking at slightly different age groups? Especially considering CVD is more common in people over 50, the risk of developing it increases throughout age.

Authors' reply: This is a valid point. Whilst the populations in the two studies overlap significantly, we could only start the current study in 2006, a limitation caused by the Prescribed Drug Register only being available for use since July 1st, 2005. This meant that the youngest participants in the study

were now 5 years older than they had been in the earlier study that started in January 2001. However, in the original study, the most protective estimates were found in older age groups.[12]

23. Reviewer comment: Looking at the main outcomes, hypertension, dyslipidaemia and diabetes mellitus, were these stratified appropriately? People with diabetes are more likely to suffer from all three conditions, was this controlled for?

Authors' reply: We considered each outcome separately. Regarding the potential effect of dog ownership potentially mediated through diabetes, we have chosen to estimate the total effect of dog ownership and not only the direct effect, which would be the interpretation if controlling for diabetes. This has been clarified in the methods section:

New text (page 7): Each outcome was considered separately as we chose to estimate total effect of dog ownership and not only the direct effects.

Results and Discussion

24. Reviewer comment: On the whole, information from results, discussion and data tables is clear, and trends support the conclusions. Line 27 (page 9)- 'During 10,692,258 person-years of follow-up, dog ownership was associated with a 2% higher risk of initiation of anti-hypertensive drug medication in both crude and multivariable adjusted analyses..'

Authors' reply: Thank you for the positive comments regarding the results, discussion and data tables. We have made the suggested change on page 9.

25. Dog ownership when? At any time? Over a long time period? Was a minimal time period set? As someone may have been only a brief time owning a dog? How dog ownership was measured and structured in analysis needs to be clearer in methods and presentation of results.

Authors' reply: This is an important issue that has now been clarified in the methods:

New text (page 6): Exposure to dog ownership was time-updated to include only those periods where each dog was alive and registered to the study participant or their registered partner.

26. Reviewer comment: Line 7 (page 11) - We know that owners of companion/toy breeds are likely to walk dog less and therefore have a lower overall physical activity. This is mentioned in line 49 'The level of dog walking might be lower in the smaller companion/toy dogs breeds as compared to the hunting-type breeds.¹⁹ In TwinGene, 68% of hunting breed owners reporting a high level of physical activity versus 52% in non-dog owners.' This sentence needs moving up two paragraphs to line 7.

Authors' reply: We have made the appropriate changes on page 11.

27. Reviewer comment: Have authors thought about doing a mediation analysis or controlling for physical activity? What happens to the dog ownership variable subsequently?

Authors' reply: This would have been a good way to clarify the associations however, we could not control for physical activity because we did not have sufficient information in the database. Information on exercise was available in the original SALT study from which the TwinGene sub-study was derived. It was not included in the TwinGene questionnaire. However, we decided against using it because the information was between 2 to 10 years old at TwinGene study baseline was conducted and we could not account for changes in lifestyle during the period between the two studies.

28. Reviewer comment: Line 26 (page 12) - the possible misclassification of dog ownership was also present in the main study; is this not a great potential limitation? Further limitations include no information on dog walking, physical activity levels or dog attachment. Studies have shown these factors are likely to be important mediators between dog ownership and health outcomes.

Authors' reply: Thank you; we have now clarified this statement on page 13:

New text (page 13): The register-based nature of our study made it impossible to account for pet-associated factors such as primary pet responsibility, physical activity related to dog walking, the level of dog attachment or indeed the reason for acquiring a dog.

New text (page 13): A smaller study population, although not selected in relation to exposure or outcome, and possible misclassification of dog ownership (due to no information on partners' dog ownership) or lifestyle questionnaire data (collected some years earlier) were important limitations in the subcohort analyses. Misclassification of dog ownership was also possible in cohabiting partners without children in common, as these would not be registered as cohabiting in the Register of The Total Population.

29. Reviewer comment: Other limitations (I think) include not fully accounting for the time or length of dog ownership. It is also not clear whether the dog ownership data is particularly reliable in the main study. For example how good are people at notifying that their dog has died?

Authors' reply: Thank you for these insightful comments.

We have made the appropriate changes to the exposure section of the methods section:

New text (page 6): Exposure to dog ownership was time-updated to include only those periods where the dog was alive and registered to the study participant or their registered partner. Hence, we try to capture the association of current dog ownership with risk of initiation of treatment for cardiovascular risk factors.

With regards to dog registration, out of 295,682 participants included in the study, we extrapolated the registration of partners' registration onto study participants from 126,465 partners. This was possible because partner information is updated annually in the Register of the Total Population. By linking the partners information to the Dog registers' we could extract information on the start of registration, age of the dog, change of ownership and death where reported. It is government legislation that all dogs be registered in Sweden, and stray dogs are extremely rare.

From the 295,682 registered dog owners, dog ownership was changed to a different owner in 5,822 (2.0%) dogs and 14,803 (5.0%) owners were recorded as having a dog that died during the study period. In addition, 174,167 (58.9%) dogs were born between the start of the study on 1st October 2006 and the end of the study on 31st December 2012. We extrapolated a date of dog death (10 years after date of birth) on all but the dogs registered as dead or had changed ownership. We have now also rerun all analysis assuming death at age 8 and 12, yielding very similar results. These results are presented in Supplementary Table 6.

New text (page 6): If information on a dog's death was missing, we assumed a maximum lifespan of ten years.[13] We conducted sensitivity analyses examining associations with dog death at a maximum lifespan of 8 years and 12 years.

New text (page 11): Sensitivity analyses on changing the maximum lifespan of dogs that had no dates of death to 8 years or 12 years yielded similar results to the maximum of 10 years (Supplementary Table 7).

Supplementary Table 7: Association of dog ownership with initiation of medication for hypertension, dyslipidemia and diabetes. Shown for assuming 10-year life-span and a sensitivity analyses at 8-year and 12-year dog life-span.

Medication Assuming 10-year life-span of dog Assuming 8-year life-span of dog Assuming 12-year life-span of dog

Sex-age adjusted model *Fully-adjusted model Sex-age adjusted model *Fully-adjusted model Sex-age adjusted model *Fully-adjusted model

Hypertension 1.02 (1.01-1.03) 1.02 (1.01-1.03) 1.02 (1.01-1.03) 1.01 (1.00-1.02) 1.03 (1.02-1.04) 1.02 (1.01-1.03)

Dyslipidemia 1.03 (1.02-1.04) 1.02 (1.01-1.04) 1.02 (1.01-1.04) 1.02 (1.00-1.03) 1.03 (1.02-1.04) 1.02 (1.01-1.04)

Diabetes 0.91 (0.89-0.94) 0.98 (0.95-1.01) 0.90 (0.88-0.93) 0.97 (0.94-1.00) 0.92 (0.90-0.94) 0.99 (0.96-1.02)

*Fully-adjusted models adjusted for sex, age, type of family, area of residence, population density, marital status, education level and latitude of residence

30. Reviewer comments: The unavailable information on comorbidity, disability and body mass index is a major flaw (national cohort) and could be mentioned again in the limitations section. Authors could attempt to explain/mention other potential mechanisms of the pet effect e.g. increased social well-being, decreased psychological stress, and immune system development, as additional reasons why dog ownership could offer protection against cardiovascular disease and death.

Authors' reply: Thank you for highlighting these limitations. The following statements have been added to the discussion section in different parts on pages 12 and 13:

New text (page 13): A previous study in this population showed a lower risk of cardiovascular and all-cause mortality in dog-owners.[12] The current study suggests that it is unlikely that hypertension and dyslipidemia mediates these effects. Other potential factors that may explain this reduction in mortality include increased social well-being and decreased psychological stress.

New text (page 13): At the same time, while national registers allow for large and unselected populations with no loss to follow-up, they lack information on individual attributes such body mass index, blood pressure, lipid levels and physical activity. A strength of this study was that we were able to include additional clinical, health measurements and socioeconomic variables using data from the TwinGene study supporting the presence of additional confounding of the relationship between dog ownership and cardiovascular risk factors from employment status and non-CVD comorbidities.

New text (page 13): The main limitation of the study is the possibility of remaining unmeasured confounding by unmeasured socioeconomic factors or pre-existing personality traits. Further, the register-based nature of our study made it impossible for us to account for pet-associated factors such as primary responsibility for care, physical activity related to dog walking, the level of dog attachment or indeed the reason for acquiring a dog.

31. Reviewer comments (Table 1): Line12 (pg16) - Dog owners here are individuals who had a registered dog at any time point during the study period; however this may not be a time period close

to when individuals have a health condition, nor for very long? This leads me to the questions I have raised regarding dog ownership measurement and potential limitations that are currently not clear.

Authors' reply: We apologize for being unclear. The descriptive table summarizes baseline characteristics for those with dogs at any time during the study. However, the Cox regression analysis uses time-updated measurement.

New text (page 6): Exposure to dog ownership was time-updated to include only those periods where each dog was alive and registered to the study participant or their registered partner.

32. Supplementary Table 1. Reviewer comment: Line 4 (page 27)- Edit large space in variable created column in regards to exercise

Authors' reply: We have made the appropriate changes.

33. Supplementary Table 3. Reviewer comment: Line 8 (p9 29)- 'XX' needs defining

Authors' reply: We have made the appropriate changes.

34. Supplementary Table 5. Reviewer comment: Line 9 (p6 30)- 'dog ownership status on the date of clinical examination and other non-clinical details extracted from the SALT questionnaire (1998-2002)'- I am a little confused as to the time point of dog ownership measurement and whether this is concurrent with when exercise was measured.

Authors' reply: We are sorry about the lack of clarity and have rephrased the text as follows:

New text (page 6): Clinical information was taken during TwinGene study (2004-2008), dog ownership status derived from registers on the date of clinical examination, and employment, profession and type of housing was extracted from the SALT questionnaire (1998-2002). All variables taken from SALT are described in Supplementary Table 1.

35. Supplementary Figure 3 Reviewer comment: Not easy to interpret and therefore does not really add value, is there a clearer way of portraying this?

Authors' reply: We used the direct acyclic graph to show our a priori assumptions about the relationship between dog ownership and the three independent different risk factors. The graph is a tool for illustrating causal and biasing paths where the biasing paths should be closed, for instance by covariate adjustment. We believe that presenting the figure is useful showing the choice of variables considered and available and would therefore like to keep it as a Supplementary figure. We have increased the size of Supplementary Figure 3 to provide better visibility of the variables and direction of the arrows. If the Editor also thinks it is better to omit this figure, we are ready to reconsider.

Reviewer: 2

Reviewer Name: Erika Friedmann

Institution and Country: University of Maryland, USA

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The paper presents an interesting analysis of an excellent data source, a national health registry that can be linked to files that include pet ownership. The longitudinal nature of the data and the use of the twin data enhance the value and complexity of the analysis.

1. Reviewers comment: I am concerned about the use of so many predictors as confounders/covariates in the analysis in the sense that many of them may be related not only to the outcome but also to likelihood of pet ownership. For example employment status, income, area of residence, marital status, presence of children in the household all may be predictors of dog ownership. Thus the study suffers from the problems typical of cohort studies being used to evaluate the effects of "interventions" that were not part of the study design. Propensity analysis or marginal structural models are modern modelling techniques that would enhance the approach to enable better evaluation of the actual impact of pet ownership as a "intervention" to reduce incidence of medication.

Authors' reply: Thank you for your detailed comments. Selecting the appropriate number of confounders to be included as covariates in the analysis is always an important and difficult task. We applied the approach where we in a causal diagram (directed acyclic graph; DAG) illustrate potential causal pathways (Supplementary Figure 3).[14] The task is then to close any biasing paths caused by confounding, where employment status, income, area of residence, marital status and presence of children in the household (directly or indirectly) both influences the probability of owning a dog and the probability of the outcome and would thus serve as confounders. The standard Cox regression methods, as applied in our manuscript, will estimate the association between dog ownership on the outcomes at the mean values (or reference category of a categorical variable) of these confounders. The number of covariates that can be included in a Cox model is partly dependent on the number of outcomes (a rule of thumb is at least 10 outcomes per variable in the model);[15] however, with the large study population and large number of outcomes, this would rarely be a problem. Although we do agree that it would be interesting to apply causal inference methods such as propensity score matching or marginal structural models on our data, we think that for the present manuscript, we would like to focus on the standard epidemiological methods. However, to evaluate if the results would differ much with a propensity score adjustment, we calculated a propensity score for dog ownership based on the same confounders as were adjusted for in our main analysis. The propensity score adjustment has some advantages compared to the ordinary covariate adjustment, however our results overlapped those obtained in the Cox regression analysis as presented in the following table:

Reviewer Table 1. Association of dog ownership with initiation of medication for hypertension, dyslipidemia and diabetes. Results reported as hazard ratios (HR) and 95% confidence intervals (CI).

*Propensity Score Models §Cox Regression Models

Medication	HR (95%CI)	HR (95%CI)
Hypertension	1.03 (1.02-1.04)	1.02 (1.01-1.03)
Dyslipidemia	1.04 (1.02-1.05)	1.02 (1.01-1.04)
Diabetes	0.98 (0.96-1.01)	0.98 (0.95-1.01)

*Propensity scores calculated as the conditional probability of dog ownership given sex, age, type of family, area of residence, population density, marital status, region of birth (Sweden, Nordic, and Non-Nordic), income, education level, latitude of residence.

§Cox Models adjusted for sex, age, type of family, area of residence, population density, marital status, region of birth (Sweden, Nordic, and Non-Nordic), income, education level, latitude of residence.

We also agree that using available data sources for epidemiological research questions does pose some problems when it comes to the availability of potential confounders in the databases. By assessing the association between dog ownership and outcomes in two databases, the national cohort and the TwinGene cohort, we try to overcome some of these limitations. In response to the comments by the reviewer, we have expanded on these issues in the discussion.

New text (page 13): At the same time, while national registers allow for large and unselected populations with no loss to follow-up, they lack information on individual attributes such body mass index, blood pressure, lipid levels and physical activity. A strength of this study is that we were able to include additional clinical health measurements and socioeconomic variables using data from the TwinGene study supporting the presence of additional confounding of the relationship between dog ownership and cardiovascular risk factors from employment status and non-CVD comorbidities.

2. Reviewer comment: In addition, the authors did not discuss (based on other studies of the health effects of pet ownership) the possible basis for the differences in the results of their previous analysis, showing that mortality was decreased with dog ownership, and the results of this set of analyses with respect to what they might mean about the influence of pet ownership on health

Authors' reply: Thank you. We have now clarified this by adding the following statement to the discussion section of the manuscript:

New text (page 13): A previous study in this population showed a lower risk of cardiovascular disease and all-cause mortality in dog owners.[12] The current study suggests that it is unlikely that hypertension and dyslipidemia mediates these effects. Other potential factors that may explain this reduction in mortality include increased social well-being and decreased psychological stress.[16]

3. Reviewer comment: It is also not clear why they authors were interested in specific breeds of dogs - even 10 groups seems excessive. The basis for grouping the dog breeds also is unclear.

Authors' reply: Thank you. The ten breed groups were selected based on the categorization employed in the Federation Cynologique International standard with some local adaption from the Swedish Kennel Club. They are categorized based on character and behaviour, and a statement to clarify this has been added in the 'exposure' section of the methods on page 6.

New text (page 6): To define breed groups, we used the Federation Cynologique International standard with some local adaption from Swedish Kennel Club's definition to categorize the 331 breeds into ten breed groups based on character and behaviour attributes (Supplementary Table 2).

4. Reviewers comment: A minor issue Supplementary table 3 - "XX" in title should be replaced with a year.

Authors' reply: Thank you, we have made the appropriate changes.

5. Reviewers comment: It could be helpful to readers to have complete analyses, with all covariates, included as supplementary tables.

Authors' reply: Thank you. We have now included the full Cox regression output with the estimates for all covariates in the models, now provided as Supplementary Table 8, Supplementary Table 9 and Supplementary Table 10. A reference statement is also included in the main text.

New Text (page 11): To provide additional information, the output from the fully adjusted Cox regression models for the association of dog ownership with the initiation of medication for hypertension, dyslipidemia and diabetes mellitus in the national cohort are included in the supplementary material as Supplementary Table 8, Supplementary Table 9 and Supplementary Table 10, respectively.

FORMATTING AMENDMENTS (if any)

Required amendments will be listed here; please include these changes in your revised version:

- Kindly re-upload each figure under 'Image' file designation' with at least 300 dpi resolution and at least 90mm x 90mm of width.

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VERSION 2 – REVIEW

REVIEWER	Carri Westgarth University of Liverpool, UK
REVIEW RETURNED	17-Oct-2018

GENERAL COMMENTS	<p>Thanks for such comprehensive revisions that improve this interesting paper. I have a few suggestions for minor revisions.</p> <p>Hunting breeds analysis - is there a better way to describe these breed types than 'hunting'? As it does not contain all hunting dogs, and may lead to people assuming that hunting breeds are better for human health (especially when reported by media). I think the issue here is perhaps these are dog breeds that are perceived as active and requiring significant physical activity, hence they are walked more. It is not that they are breeds used for hunting. I think revision of the description of the breed groups would make for a clearer papers and media reporting.</p> <p>Abstract - the conclusion of the abstract is slightly different to that of the paper in regard to the findings. Paper says DO associated with minimally higher risk of initiation of treatment for hypertension and dyslipidemia, and hunting breed types associated with lower risk of initiating treatment for diabetes. Abstract says DO not associated with any large reduction in initiation of medication for classical cardiovascular risk factors...</p> <p>Although this is sort of the same thing as above, I think it would be clearer to make the conclusions consistent in wording.</p> <p>Abstract- it also isn't clear in the abstract that your analyses is based upon medication prescriptions. This can be added to the 'main outcome measures' section.</p> <p>Please could you add a bit more description to the methods section about the registration of dogs. Many countries register dogs but the uniqueness of Sweden to be able to perform such as study appears to be that compliance to the registration of dogs is high. You comment to this effect in your reviewers response but it needs adding to the methods in the paper. Please add some</p>
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	<p>statement and preferably evidence that the proportion of unregistered dogs is low.</p> <p>It is also unclear in the methods section that it was not possible to identify people who cohabit but are not married/civil partnership or have children. It mentions in the limitations section in the discussion that this is a limitation (here it would be good to add what proportion of the population this is thought to be). Please also clarify in the methods that your procedure does not capture these 'partners'.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer Name: Carri Westgarth

Institution and Country: University of Liverpool, UK.

Please state any competing interests or state 'None declared': None declared.

Thanks for such comprehensive revisions that improve this interesting paper. I have a few suggestions for minor revisions.

Reviewer comment: Hunting breeds analysis - is there a better way to describe these breed types than 'hunting'? As it does not contain all hunting dogs, and may lead to people assuming that hunting breeds are better for human health (especially when reported by media). I think the issue here is perhaps these are dog breeds that are perceived as active and requiring significant physical activity, hence they are walked more. It is not that they are breeds used for hunting. I think revision of the description of the breed groups would make for a clearer papers and media reporting.

Authors' reply: The authors would like to acknowledge the insightful comments and detailed review that helped to improve the manuscript. We have revised the description of the Terriers, Pointing, Scent hounds and Retrievers from hunting breed types to 'active dog breeds'; with a statement that clarifies that we identified these breeds in our previous research and will use this term throughout the manuscript.

New text page 7: Based on previous findings [3] that ownership to four different breed groups was associated with a lower risk of cardiovascular events, we defined a group of these dog breeds (Terriers, Pointing, Scent Hounds and Retrievers) for additional exploratory analysis. This group is hereafter referred to as 'active dog breeds' as these breeds also generally demand high levels of physical activity.

Supplementary figure 4 page 17: Figure revised to denote the first breed groups as "active dog breeds instead of hunting breeds.

Reviewer comment: Abstract - the conclusion of the abstract is slightly different to that of the paper in regard to the findings. Paper says DO associated with minimally higher risk of initiation of treatment for hypertension and dyslipidaemia, and hunting breed types associated with lower risk of initiating treatment for diabetes. Abstract says DO not associated with any large reduction in initiation of medication for classical cardiovascular risk factors...

Although this is sort of the same thing as above, I think it would be clearer to make the conclusions consistent in wording.

Authors' reply: Thank you, the conclusion in the abstract on page 2 has been revised to mirror the one in the main manuscript.

New text page 2 (conclusion in Abstract): In this large cohort study, dog ownership was associated with a minimally higher risk of initiation of treatment for hypertension and dyslipidemia implying that the previously reported lower risk of cardiovascular mortality among dog owners in this cohort is not explained by reduced hypertension and dyslipidemia. These observations may suffer from residual confounding despite access to multiple important covariates, and future studies may add valuable information.

Reviewer comment: Abstract- it also isn't clear in the abstract that your analyses is based upon medication prescriptions. This can be added to the 'main outcome measures' section.

Authors' reply: Thank you. The appropriate change has now been made to the main outcome measures section of the abstract on page 2.

New Text page 2: Initiation of medication for hypertension, dyslipidemia and diabetes mellitus.

Reviewer comment: Please could you add a bit more description to the methods section about the registration of dogs. Many countries register dogs but the uniqueness of Sweden to be able to perform such as study appears to be that compliance to the registration of dogs is high. You comment to this effect in your reviewers response but it needs adding to the methods in the paper. Please add some statement and preferably evidence that the proportion of unregistered dogs is low.

Authors' reply: Thank you. The appropriate changes have been made on page 6.

New text page 6: Dogs in Sweden are required to have a unique identifier (ear tattoo or implanted identity chip) and this is registered alongside their owner's unique personal identity number at the Swedish Board of Agriculture. All dogs sold as purebred are registered by the Swedish Kennel Club.

In Sweden, there are virtually no stray dogs,[29] and compliance to regulations is thought to be high due to a general high level of social and institutional trust.[30]

Reviewer comment: It is also unclear in the methods section that it was not possible to identify people who cohabit but are not married/civil partnership or have children. It mentions in the limitations section in the discussion that this is a limitation (here it would be good to add what proportion of the population this is thought to be). Please also clarify in the methods that your procedure does not capture these 'partners'.

Authors' reply: Thank you, the appropriate changes have been made on page 6.

New text page 6: The identification of partners was possible through annual extracts from the Register of the Total Population that keeps track of couples that are married, registered in same-sex partnership or are cohabiting with common children. It is presently not possible to identify non-married cohabiting partners who have no children in common in the population registers.

VERSION 3 – REVIEW

REVIEWER	Carri Westgarth University of Liverpool, UK
REVIEW RETURNED	07-Nov-2018
GENERAL COMMENTS	Thank you for addressing my minor concerns on the latest version of the paper. I think it is a really interesting contribution to the field.