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**«ΜΕΘΟΔΟΛΟΓΙΑ ΕΡΕΥΝΑΣ
ΣΤΙΣ ΒΙΟΪΑΤΡΙΚΕΣ ΕΠΙΣΤΗΜΕΣ, ΤΗΝ ΚΛΙΝΙΚΗ ΠΡΑΞΗ ΚΑΙ ΤΗ
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ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

Pet exposure and survival of older adults: Evidence from the Survey of Health, Ageing and Retirement in Europe (SHARE)

ΚΩΝΣΤΑΝΤΙΝΟΣ ΧΡΙΣΤΟΠΟΥΛΟΣ

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Ευχαριστίες

Θα ήθελα να ευχαριστήσω τον επιβλέποντα καθηγητή μου κ. Νικόλαο Πανταζή για την αρμονική συνεργασία που είχαμε κατά την εκπόνηση της εργασίας καθώς και την καθηγήτρια κα. Βασιλική Μπενέτου για τις συμβουλές και διαθεσιμότητα της. Ευχαριστώ επίσης την Έλενα Ριζά για τα σχόλια και τις προτάσεις της. Τον Χρήστο Σκουρλά για την ψυχολογική και συμβουλευτική υποστήριξη του. Τέλος, ευχαριστώ όλους τους ανθρώπους που συνεισφέρουν αφιλόκερδος στην δημιουργία κώδικα και ελεύθερου λογισμικού καθώς και στα σχετικά φόρουμ.

Περίληψη

Εισαγωγή: Η διαρκώς αυξανόμενη κατοχή κατοικίδιων ζώων εκθέτει εκατομμύρια ανθρώπους σε αυτόν τον περιβαλλοντικό παράγοντα. Παρότι η συσχέτιση αυτή έχει μελετηθεί αρκετά δεν υπάρχει επαρκής τεκμηρίωση σχετικά με την επίδραση που μπορεί να έχουν τα κατοικίδια ζώα στην υγεία του ανθρώπου.

Στόχος: Η μελέτη της πιθανής συσχέτισης της κατοχής κατοικίδιων ζώων (οποιουδήποτε κατοικίδιου, γάτα, σκύλος, πτηνό, ψάρι) με τη θνησιμότητα από όλες τις αιτίες, τη θνησιμότητα από καρδιαγγειακά νοσήματα και από κακοήθεις νεοπλασίες στον πληθυσμό ηλικίας 50 ετών και άνω που ζει στην Ευρώπη.

Μέθοδοι: Συνολικά 23,274 άνδρες και γυναίκες, μέσης ηλικίας 64.2 ετών (SD: 9.8 έτη) από 15 Ευρωπαϊκές χώρες, εθελοντές στη μελέτη Survey of Health Ageing and Retirement in Europe (SHARE) συμμετείχαν στη μελέτη. Η θνησιμότητα από όλες τις αιτίες (5163 θάνατοι), από καρδιαγγειακά νοσήματα (1832 θάνατοι) και από κακοήθεις νεοπλασίες (1346 θάνατοι) μελετήθηκαν με την χρήση μοντέλων Cox αναλογικών κινδύνων, για την ανεύρεση πιθανής σχέσης με την έκθεση σε κατοικίδια ζώα (που καταγράφηκε κατά την πρώτη συνέντευξη). Επίσης, διαστρωματοποιημένες αναλύσεις διεξήχθησαν ανά φύλο και ανά μέγεθος νοικοκυριού.

Αποτελέσματα: Δεν παρατηρήθηκαν στατιστικά σημαντικές συσχετίσεις για κανένα από τα κατοικίδια σε σχέση με τη θνησιμότητα από όλες τις αιτίες. Ωστόσο, στις διαστωματοποιημένες αναλύσεις, η έκθεση σε πτηνά βρέθηκε να αυξάνει τον κίνδυνο της θνησιμότητας από όλες τις αιτίες στις γυναίκες [Hazard Ratio (HR) = 1.23, 95%CI: 1.04 – 1.44] καθώς και στις γυναίκες που διέμεναν μόνες [HR = 1.38, 95%CI: 1.02 – 1.85]. Αυξημένος κίνδυνος θανάτου για αίτια εκτός των καρδιαγγειακών και των κακοήθων νεοπλασιών [HR = 1.40, 95%CI: 1.05 – 1.99] βρέθηκε για τις γυναίκες ιδιοκτήτριες πτηνών σε σχέση με τις μη ιδιοκτήτριες πτηνών.

Συμπεράσματα: Η έκθεση σε πτηνά μπορεί να έχει αρνητική επίδραση στην επιβίωση του γυναικείου πληθυσμού μεγαλύτερης ηλικίας στην Ευρώπη.

Abstract

Background: With pet ownership on the rise, millions of individuals are exposed to this environmental factor. Nevertheless, more evidence is needed in order to clarify the potential association of pet ownership with human health.

Objective: To study the association of pet exposure (any pet, cat, dog, bird, fish) with all-cause mortality, cardiovascular and cancer-specific mortality in Europeans over the age of 50.

Methods: A total of 23,274 men and women, aged 64.2 years ($SD:$ 9.8) from 15 European countries, volunteers in the Survey of Health Ageing and Retirement in Europe (SHARE) participated in this study. All-cause mortality (5,163 deaths), cardiovascular disease (CVD) mortality (1,832 deaths) and cancer-specific mortality (1,346 deaths) were examined, using Cox Proportional Hazards models, for their relation with pet exposure assessed at baseline. Stratified analyses were also performed by gender and for single or multi-person households.

Results: No significant association was observed for any of the pets ownership with all-cause mortality. In stratified analyses, exposure to birds increased total mortality in females [Hazard Ratio (HR) = 1.23, 95%Confidence Intervals (CI) (1.04-1.44)] and in females living alone [HR = 1.38, 95% CI (1.02-1.85)]. Female bird owners had increased risk of death for causes other than cancer and CVD [HR = 1.40, 95%CI (1.05-1.99)].

Conclusions: Bird exposure may have a negative impact on the survival of older female population leaving in Europe.

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1 Introduction

Human and non-human animals have coexisted for thousands of years. In past times, their relationship revolved around daily work and husbandry, but in recent years, companionship has been one of the main purposes for ownership. Worldwide, the numbers of household pets have been increasing and hence a booming industry has risen to fulfil the sometimes artificial/humanised needs of the pets. In Europe, rough estimates suggest that 38% of European households own at least one pet, with cats being the most prevalent (in numbers) followed by dogs, birds and other mammalian, aquatic, and reptilian animals (FEDIAF, 2020).

This trend has led several researchers to study the potential associations, mainly beneficial, of pet exposure on the health and longevity of their owners. As a result, many observational studies have been published related to physical (Curl et al., 2016; Mičková et al., 2019; Parslow et al., 2005; Raina et al., 1999; Taniguchi et al., 2018) or mental health (Colombo et al., 2006; Enmarker et al., 2015; Friedmann et al., 2011; Garrity et al., 1989; Parslow et al., 2005; Powell et al., 2019; Raina et al., 1999; Taniguchi et al., 2018) and exposures ranging from in utero (Xu et al., 2020) to late years (Scheibeck et al., 2011). However, the majority of the existing research is cross-sectional, hence robust evidence is limited. On the other hand, researchers have also identified potential hazards associated with pet ownership such as allergies (Hölscher et al., 2002), zoonotic diseases (Grant and Olsen, 1999), the increased risk of falls in older individuals (Kurrle et al., 2004) and bite injuries with or without subsequent infection (Feldman et al., 2004).

Pet-wise, dogs had the lion's share in the relevant literature with findings suggesting beneficial health effects. The potential increase in the physical activity of their owners, mediated though dog walking, is a factor that is lacking in other types of pets (Curl et al., 2016). Subsequently, the effect on cardiovascular (CVD) outcomes and the their associated risk factors, such as blood pressure, body mass index (BMI) and stress, have been particularly studied.[1] Another advantage of dog walking is increased exposure to nature which may yield additional benefits to health (Zijlema et al., 2019). There is also evidence for improvements in mental health such as reduction in depression (Le Roux and Kemp, 2009), anxiety (Hoffmann et al., 2009), and some vague evidence on decrease sense of loneliness (see Gilbey and Tani (2015) for a discussion), as well as a boost in the self-esteem of their owners (Schulz et al., 2020). Some of the effects on mental health may be mediated partially by social interactions occurring during dog walking (Antonacopoulos and Pychyl, 2014). Based on the aforementioned, it is no surprise that a huge Danish case-control study found an 8% decrease in all-cause mortality for dog owners (Sørensen et al., 2018).

Cats are most of the times studied in conjunction with dogs. When studied on their own the research usually revolves around allergies and asthma. There is significant evidence that childhood and adolescence exposure in cats can have a protective role against asthma, atopy, allergic rhinitis, pneumonia, and bronchiolitis is later life (de Meer et al., 2004; Hesselmar et al., 1999; Roost et al., 1999; Stokholm et al., 2018). On the other hand, cat ownership has been linked with an increased risk of female lung cancer (Adhikari et al., 2019).

For birds and fish, some research has been carried out in the context of animal-assisted therapy for the elderly (Edwards and Beck, 2002; Colombo et al., 2006). Bird ownership was also studied in the 90s in case-control settings for a potential link with lung cancer with inconsistent results (Alavanja et al., 1996; Gardiner et al., 1992; Kohlmeier et al., 1992; Modigh et al., 1996; Morabia et al., 1998). This research topic was fuelled from an earlier Dutch case-control study which found a massive increase in risk (6.7 fold) in bird owners (Holst et al., 1988). A more recent and more robust study by Adhikari et al. (2019) indicates that the risk is real yet not so elevated.

The mental and physical health of older individuals has been a particular focal point,

[1] See Arhant-Sudhir et al. (2011) for a review.

perhaps due to the increased frailty of the elderly. The quality of life of older populations is additionally important since their share in the demographic pie constantly increases. Hughes et al. (2020) provide a systematic review which highlights the beneficial effect in various mental health outcomes as well as evidence for improved CVD risk factors, amongst pet owners. Pets, and dog in particular, may be also beneficial for socially isolated older adults during the COVID-19 pandemic (Ikeuchi et al., 2021), and might even reduce the frailty incidence risk of their walkers during periods of population mobility-limiting mandates (e.g. lockdown measures) (Taniguchi et al., 2019). It is worth mentioning again, that the study design of most of the literature is cross-sectional and more robust evidence is necessary even for arguments one may consider settled or self-evident. Flegr and Preiss (2019) also make a case for eliminating the volunteer bias which is present in many studies. Self-selection of pet owners may also lead to an error in the measurement of their self-perceived health status, when they are informed about the aim of the study.

A methodology with a clear time dimension is the time-to-event (TTE) analysis. These methods provide more robust evidence although some pitfalls exist.[2] Most TTE studies have death as the event of interest, hence the other, more common name, survival analysis. In the case of pets, even with a TTE analysis, several difficulties lie in the measurement of the exposure and interpretation of the results (more discussion later in the paper). Nevertheless, all-cause, non-established CVD[3] and cancer mortality have been studied with regard to pet exposure. The studies concern predominantly US or northern European populations, hence their generalisability is limited.

Several survival studies have shown no association of dog or cat exposure with all-cause mortality (Ding et al., 2018; Qureshi et al., 2009; Torske et al., 2017; Gillum and Obisesan, 2010). Mubanga et al. (2017) provides the only study where all-cause mortality is inversely

[2]See Hernán (2010) for a discussion.

[3]Studies for established CVD also exist (see for example Chowdhury et al., 2017; Mubanga et al., 2019). See also Kramer et al. (2019) for a review on dog ownership and CVD survival.

associated with dog ownership, although no lifestyle controls were included in the analysis. The evidence is limited for a protective association against CVD mortality in dog owners. In two large sample survival studies, Ding et al. (2018) in England found no association, while Mubanga et al. (2017) in Sweden found a large protective effect (HR=0.64). Interestingly enough, Qureshi et al. (2009) argue that *past* cat ownership is inversely associated with CVD and Myocardial Infraction (MI) deaths. Ogechi et al. (2016) also found a very protective association against CVD and stroke deaths in current (at baseline) cat owners. Because the number of events in these last studies is very limited, further investigation is required.

Cancer mortality has also been the subject of investigation, although no association was found in cancer incidence of female owners by Garcia et al. (2016). The subject has only been studied in US population samples using the National Health and Nutrition Examination Survey (NHANES) III data. As mentioned previously, cat or bird ownership was associated with lung cancer in females (Adhikari et al., 2019). Furthermore, cat exposure was also linked with increased risk of colorectal cancer (Adhikari et al., 2020). Buck et al. (2020) examining all-cancer mortality also found an increased risk for female cat or bird owners, probably a result of the hazards described in the two previous cancer-specific studies.

This study aims to explore whether pet exposure (any pet exposure such us, dog, cat, bird, fish, as well as combinations of those) assesed at baseline is associated with the survival among older European residents. To this end, we model the all-cause, CVD, and cancer mortality using data from the SHARE project (Börsch-Supan et al., 2013). Compared to previous studies which used large sample but were limited at national level, this study has the advantage of using individuals from a diverse set of European countries thus improving its external validity. Moreover, a vast set of cross-country comparable important variables were available and also tested for unobserved heterogeneity.[4]

[4]Unobserved heterogeneity refers to the inter-individual differences that are not measured by the regressors.

2 Materials & Methods

2.1 The SHARE project

The SHARE project[5] is an ongoing longitudinal household survey of European residents which started in 2004 and is performed approximately every 2 years. It focuses primarily on individuals over the age of 50 but younger participants are also included in case of cohabitation. The survey uses a probability sample, although the sampling framework varies between countries.[6] The data are collected via computer-assisted personal interviews (CAPI) and participation rates, although highly variable between countries, were approximately[7] 60% and 50% for household and individual, respectively (Bergmann et al., 2017). Additionally, a self-completion drop-off questionnaire containing more sensitive questions is distributed to participants. The response rate for this was 81% on average for the first wave (Bergmann et al., 2017).

All the data for our analysis were extracted from the SHARE databases[8] of waves 1 through 8. According to the methodology book (Börsch-Supan and Jürges, 2005) 'SHARE underwent a thorough review of ethical standards by the University of Mannheim's internal review board (IRB)'. The validity, reliability and final translation of the questionnaire were

[5]The SHARE data collection has been funded by the European Commission, DG RTD through FP5 (QLK6-CT-2001-00360), FP6 (SHARE-I3: RII-CT-2006-062193, COMPARE: CIT5-CT-2005-028857, SHARELIFE: CIT4-CT-2006-028812), FP7 (SHARE-PREP: GA N°211909, SHARE-LEAP: GA N°227822, SHARE M4: GA N°261982, DASISH: GA N°283646) and Horizon 2020 (SHARE-DEV3: GA N°676536, SHARE-COHESION: GA N°870628, SERISS: GA N°654221, SSHOC: GA N°823782, SHARE-COVID19: GA N°101015924) and by DG Employment, Social Affairs & Inclusion through VS 2015/0195, VS 2016/0135, VS 2018/0285, VS 2019/0332, and VS 2020/0313. Additional funding from the German Ministry of Education and Research, the Max Planck Society for the Advancement of Science, the U.S. National Institute on Aging (U01_AG09740-13S2, P01_AG005842, P01_AG08291, P30_AG12815, R21_AG025169, Y1-AG-4553-01, IAG_BSR06-11, OGHA_04-064, HHSN271201300071C, RAG052527A) and from various national funding sources is gratefully acknowledged (see www.share-project.org).

[6]See Börsch-Supan and Jürges (2005) pp.28-37 for details on the sampling procedure.

[7]Numbers vary depending on the measurement methodology.

[8]This paper uses data from SHARE Waves 1, 2, 3, 4, 5, 6, 7 and 8 (DOIs: 10.6103/SHARE.w1.800, 10.6103/SHARE.w2.800, 10.6103/SHARE.w3.800, 10.6103/SHARE.w4.800, 10.6103/SHARE.w5.800, 10.6103/SHARE.w6.800, 10.6103/SHARE.w7.800, 10.6103/SHARE.w8.800, 10.6103/SHARE.w8ca.800, see Börsch-Supan et al. (2013) for methodological details.

pre-tested in a probability subsample. SHARE has obtained all the necessary consents of the individuals whose personal data were obtained and underwent a thorough review of ethical standards by the University of Mannheim's internal review board.

2.2 Study participants

Since data on pet ownership and its components was available only in waves 1 and 2, from the drop-off questionnaires, participants who did not complete them were excluded from the study. Individuals without follow-up were also excluded, as were those under the age of 50 and those without any pet exposure information. Our final sample consists of 23,274 individuals from 15 countries, each country representing from 9.9% to 2.2% of the sample.[9] Figure 1 provides a schematic of the sample formation and inclusion criteria.

2.3 Pet exposure

Pet ownership data and its components were extracted from the baseline supplementary written questionnaire. The question regarding ownership was 'Do you currently have one or more of the following pets in your household?', with dog, cat, bird, fish, other pets and no pets in household, as available responses. The overall pet ownership dummy variable was created using information from the aforementioned questions, taking the value 1 if one of the 5 first responses was selected, and zero otherwise.

2.4 Survival data

The date of birth and entry in study were recorded at baseline. Exit from the study occurred in the case of death or due to right censoring. In case of death, all relevant information about the date and cause of death were provided by a proxy-respondent (e.g. family or household

[9]Countries include: Austria, Germany, Sweden, Netherlands, Spain, Italy, France, Denmark, Greece, Switzerland, Belgium, Israel, Czech Republic, Poland and Ireland. For more details see Table 6.

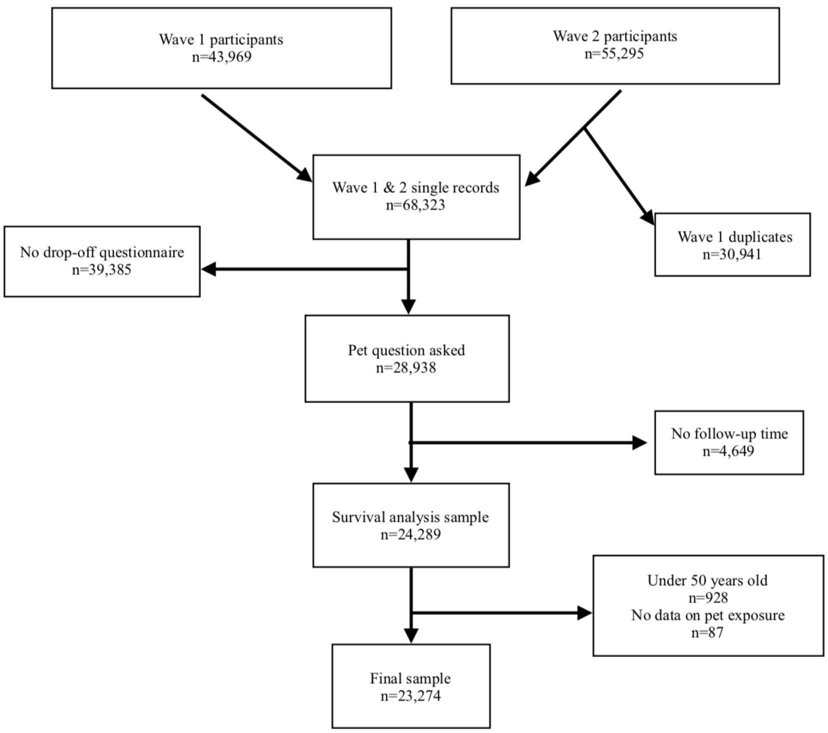

Figure 1: Flowchart for the selection of study participants

member, neighbour, friend etc.). The right censoring time point was the last interview date of the participant. The reported causes of death were re-recoded into cancer, CVD[10] and Other.[11]

2.5 Covariates

Our analysis includes a vast set of covariates including, demographic, socioeconomic, lifestyle, and medical, in an effort to control for all possible confounders. It is worth mentioning that the answers are self-reported and all covariates were measured at baseline, unless stated otherwise. Refusing, not knowing, and not remembering to answer was decoded as a missing value.

2.5.1 Identifying potential confounders

The literature on the determinants of pet ownership is very limited in number, and especially with regard to generalisability. Therefore, it provides no clear evidence as to what may confound the relationship between pet expose and survival. Nevertheless, there is some evidence that points toward education, social class, gender and age (Eller et al., 2008; Westgarth et al., 2010). Eller et al. (2008) also provide evidence for confounding by various allergic conditions. Sharpley et al. (2020) additionally show that depressed individuals had increased odds of owning a dog. Other proposed factors such as household size could also play a role, although the link with survival is not clear. Westgarth et al. (2010) propose correctly that each pet should be modelled individually, nevertheless in the absence of studies, especially for less popular pets, the task is rather difficult.

Nevertheless, an attempt was made for pet specific models in the less than the fully-adjusted specifications. Figure 2 provides the path analysis in the form of a Directed Acyclic

[10] CVD includes deaths from a heart attack, a stroke and other cardiovascular related illness.

[11] Other causes include: Respiratory disease, disease of the digestive system, severe infectious disease, accidents, and other not previously mentioned causes.

Graph (DAG) where, X and Y denote pet exposure and survival, respectively, Z represents the potential confounders, M the potential mediators, and Ω the rest of the control variables used in the analysis. The classification of the variables was based on previous knowledge and beliefs on the subject. Details on the variables follow.

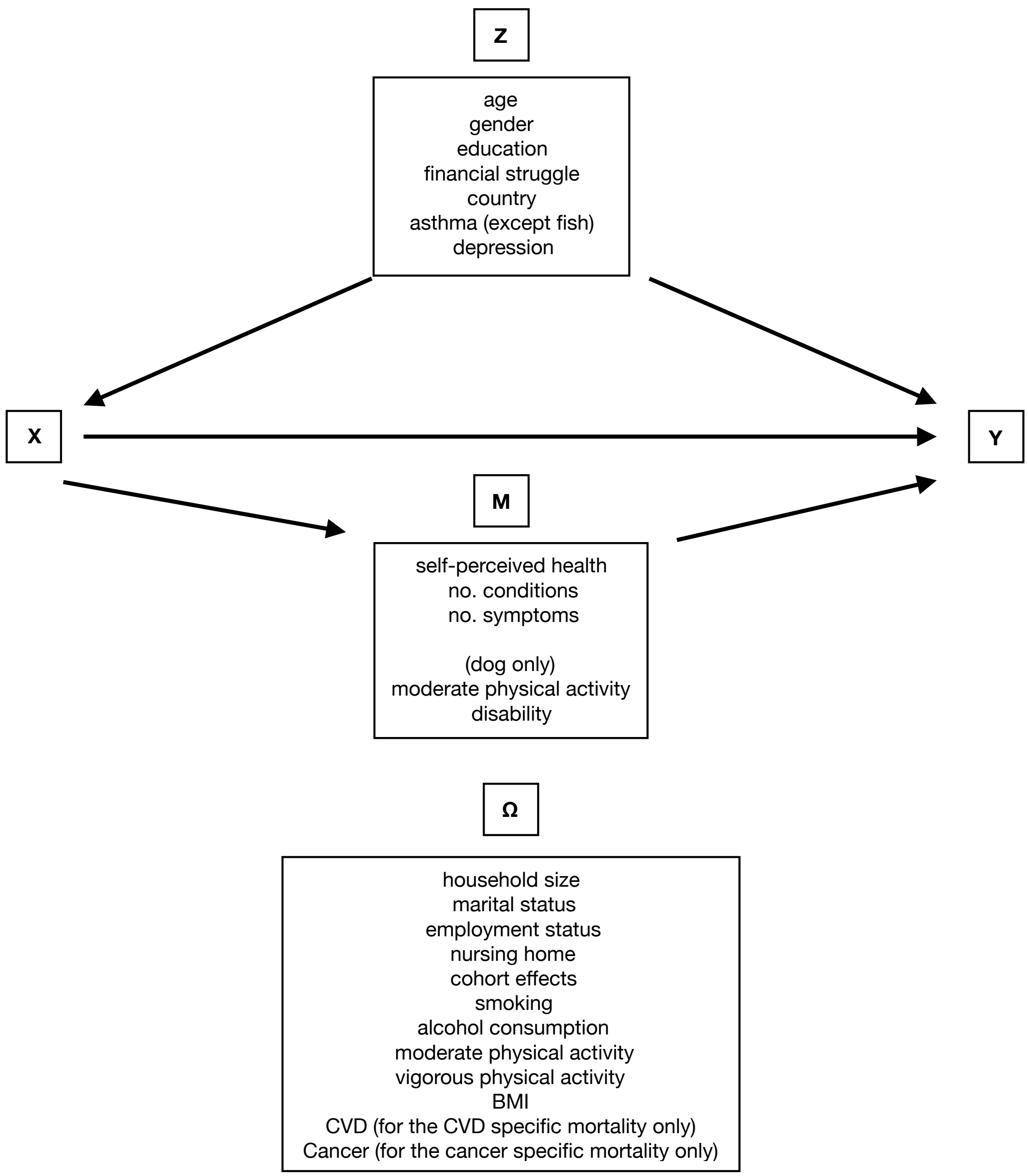

Figure 2: Directed acyclic graph for the analysis of pet exposure and survival

2.5.2 Demographic variables

Several demographic variables were included in the analysis such as: gender (male, female); age at baseline (continuous); country of residence (see Table 6), marital status (married and living together with spouse, registered partnership, married living separated from spouse, never married, divorced, widowed); been in a nursing home[12] (temporarily, permanently, no); and finally, the first wave of appearance in SHARE (wave 1 or wave 2). It is worth mentioning that age at baseline serves additionally as a control for the birth cohort effects, not explicitly modelled, in our study.

2.5.3 Socioeconomic variables

Key socioeconomic variables including household size[13] (integer > 0) and employment status (retired, employed or self-employed, unemployed, permanently sick or disabled, homemaker, other) were included. The main interest of course lies in the measurement of education and wealth. For the former, education was measured and harmonised using the 1997 International Standard Classification of Education (ISCED-97) by SHARE, and then recoded into 7 ordinal categories ranging from no education to PhD education, which were used in our analysis. Finally, the question 'Thinking of your household's total monthly income, would you say that your household is able to make ends meet?' (with great difficulty, with some difficulty, fairly easily, easily) was used as a proxy for income/wealth. This variable ensures comparability between participants from different countries since it captures the purchasing power as well as the financial struggle at the household level.

[12]Nursing homes were defined as "...institutions sheltering older persons who need assistance in activities of daily living, in an environment where they can receive nursing case, for short or long stays" and the question was 'During the last twelve months, have you been in a nursing home overnight?'. This variable could also belong to the medical covariates.

[13]A dummy variable was created to indicate single-person households, for stratified analysis.

2.5.4 Lifestyle variables

Several behavioural risk factors such as tobacco and alcohol consumption, physical inactivity and the Body Mass Index (BMI) were also included. Metric BMI was calculated from the self-reported weight and height or the respondents as kg/m^2 by SHARE, and was included as a continuous variable in our analysis. The frequency of physical activity was measured by two variables, one accounting for moderate and one for vigorous activity[14] (more than once a week, once a week, one to three times a month; hardly ever, or never). Tobacco consumption as current smoking status (yes, currently smoke; never smoked daily for at least one year; no, I have stopped), and alcohol consumption as frequency in the last 6 months (daily or almost every day, five or six days a week, three or four days a week, once or twice a week, once or twice a month, less than once a month, not at all in the last 3 months).

2.5.5 Medical information

This category includes several variables regarding the physical and mental health of individuals. The self-perceived health was also measured using the US scale (excellent, very good, good, fair, poor). Mental health was measured using the Euro-D depression scale.[15] Physical health was measured by two variables, namely the number of chronic conditions and the number of symptoms. These variables are the sum of a list of conditions and symptoms, respectively. Asthma diagnosis (yes, no) was included to control specifically for confounding from allergic conditions. Cancer or CVD diagnosis dummies were used only when modelling these specific hazards. Finally, disability was measured as a count of mobility, arm function and fine motor limitations, from a ten item list.

[14] Available responses were the same.

[15] Euro-D is a validated scale that ranges from 0 to 12 and it is used to measure geriatric depression. The factors used in the formation of the scale by SHARE include: depression, pessimism, suicidality, guilt, sleep, interest, irritability, appetite, fatigue, concentration, enjoyment and tearfulness. For more details on Euro-D see Prince et al. (1999).

2.6 Statistical analysis

The time scale used for the analysis was the attained age. This time scale is more appropriate for longitudinal surveys since it accounts for left-truncation[16] (delayed entry) and groups subjects in similar risks together (Kom et al., 1997; Thiébaut and Bénichou, 2004). Lamarca et al. (1998) also argue that this time scale is more appropriate for the survival analysis of the elderly. Despite the data being recorded in months (monthly time interval censoring), continuous time analysis was preferred due to the large median follow-up (119 months).

A model was fitted for each pet, pet interaction with another pet, as well as overall pet ownership.[17] For each of these models, four different models were employed. Model 1 controls for basic demographic factors (gender, age); Model 2 controls additionally for known confounders from the literature (education, financial struggle, country, asthma, depression); Model 3 controls additionally for potential mediators (self-perceived health, no. conditions, no. symptoms, moderate physical activity, disability); and Model 4 controls for every covariate mentioned in Subsection 2.5. Moreover, stratified analyses were performed by gender and household size, where effect modification on survival was identified in past studies (Mubanga et al., 2017). Missing values were excluded from the analysis with pairwise deletion. Missing values on the cause of death (n=380, 7.36%) were treated as censored in the cause-specific analysis at the time of death. Cluster robust standard errors were used throughout the analysis to account for the dependence at the household level.

Cox Proportional Hazards (PH) were used throughout the analysis, although Gompertz PH models also fitted the data very well. The Cox PH model is a semiparametric method that uses a partial likelihood (PL) specification for the estimation of duration data without any distributional assumptions for the baseline hazard. The model follows the standard PH

[16]Left-truncation refers to the fact that subjects were at risk at a time before they came under observation, hence in our study their inclusion in the sample is conditional to survival up to a certain age (50), resulting in selection bias.

[17]Small differences exist between pet-specific models. See Table 3 notes for details.

specification with exponential form

$$h(t, \mathbf{x}) = h_0 e^{\beta' \mathbf{x}}, \tag{1}$$

where h_0 is the baseline hazard that cancels during estimation, $\mathbf{x}$ is a vector of covariates and β the parameters. The PL[18] orders the events instead of focusing on spells, as is the case in ML estimation, assuming that for each survival time t_i there is a maximum of one event. Since ties were present in our data, we used the Breslow method which offers a good approximation if the number of events at time t_i is small relative to the persons at risk.

For every pet exposure, informal graphical checks[19] were employed to test the proportionality assumption (i.e., differences in the hazard at each time t are proportionate to differences in the regressors). Therefore, coefficients act as a scalar of the baseline survivor function. Moreover, the pet variables were included as time-varying covariates using log-time interaction terms, with no significant coefficients, signifying that the PH assumption was not violated. Finally, scaled Schoenfeld residuals were used to test more formally the H_0 of proportionality, which was not rejected. The analyses are divided in all-cause and cause-specific mortality and were performed with STATA/ MP 13.0 (StataCorp LP, TX, US).

3 Results

3.1 Sample description

The mean age of the participants at baseline was 64.2 years with a standard deviation of 9.8. Females were slightly more than males (54.2%) and the average household had 2.3 persons.

[18]PL can be defined as the joint product of the probability person i exiting, conditional on being in the risk set at $t = t_i$ over the ordered exit times.

[19]These include plotting the natural logarithm of the cumulative hazard against the natural logarithm of the survival time as well as plotting the Kaplan-Meier observed survival curves and comparing them with the Cox predicted curves.

The average participant had at least some secondary education and only 11.5% stated that their household struggles financially. Average BMI was 26.6 and only 19% were currently smokers. Some vigorous physical activity was present in 59% of the sample, while some moderate physical activity was reported in 88%. Health-wise, the average participants had 1.6 chronic conditions, 1.7 symptoms, 1.5 mobility limitations and a 2.4 score on the Euro-D depression scale, at baseline.

Table 1 presents a comparison of descriptive statistics for some key variables between pet and non-pet owners. Non-pet owners are 3 years older on average, they also have slightly higher education and better financial situation. Pet owners have slightly larger household size, worse smoking habits but better physical activity. No real differences exist in gender, BMI as well as in all the medical covariates.

3.2 Survival data

During 231,183 person-years of follow-up a total of 5,163 deaths were recorded. The mortality rate was 2.23 deaths per 100 person-years. The median survival was up to the age of 86.6 [95%CI (86.3-86.8)], while the mean follow-up was 119 months or about 12 years. For cause-specific mortality, cancer deaths were 1,346, CVD deaths were 1,832, while deaths from other causes were 1,605. Table 5 entails descriptive statistics for the survival of different pet owners.

Table 1: Selected demographic, socioeconomic, lifestyle and medical characteristics of the participants by pet ownership

		Pet owners N=13,965(60.05%)	*Non-pet owners* N=9,292 (39.95%)	*p-value*‡
Demographic				
Age (at baseline)	mean (SD)	62.17 (9.15)	65.63 (10.01)	<0.001
Gender	Male	46.56%	45.34%	0.070
	Female	53.44%	54.66%	
Household size	1	13.22%	22.82%	<0.001
	2	52.59%	56.30%	
	3+	34.19%	20.88%	
Socioeconomic				
Education (ISCED-97)†	median (IQR)	3 (3-1)	3 (3-1)	0.002
Financial management of household	with great difficulty	12.22%	11.06%	<0.001
	with some difficulty	30.29%	26.64%	
	fairly easily	34.18%	33.50%	
	easily	23.32%	28.81%	
Lifestyle				
Smoking	currently smoke	21.76%	17.21%	<0.001
	never smoked daily for at least one year	50.05%	54.10%	
	have stopped	28.19%	28.69%	
BMI (kg/m^2)	mean (SD)	26.74 (4.45)	26.45 (4.30)	<0.001
Physical activity (vigorous)	more than once a week	38.44%	34.40%	<0.001
	once a week	13.84%	13.70%	
	one to three times a month	9.36%	9.17%	
	hardly ever, or never	38.36%	42.72%	
Medical				
Depression (Euro-D)	median (IQR)	2 (4-1)	2 (4-1)	0.021
Disability (Mobility limitations count)	median (IQR)	0 (2-0)	0 (2-0)	0.034
Symptoms (count)	median (IQR)	1 (2-0)	1 (2-0)	0.343
Chronic conditions (count)	median (IQR)	1 (2-0)	1 (2-1)	0.001
Asthma diagnosis	Yes	4.80%	4.78%	0.950

Notes: † The ISCED-97 ranges from 0 to 7 with higher numbers indicating higher education. ‡ P-values for comparisons come from: mean t-tests for continuous variables, for median comparisons from Wilcoxon rank-sum tests, for dichotomous variables from Fisher's 2-sided exact test, and for ordinal categorical variables from Pearson χ^2 tests.

Table 2: Median survival with 95% CI and mortality rates for different pet exposures

	Median survival (in years)	*Mortality rate (per 1,000 person-years)*
Any pet	85.8 [85.2 - 86.3]	18.9
No pet	86.9 [86.6 - 87.2]	24.6
Cat	86.0 [85.1 - 86.8]	19.4
Dog	85.4 [84.8 - 86.1]	19.2
Bird	85.3 [84.3 - 86.3]	22.1
Fish	86.9 [85.0 - 89.6]	12.9

Notes: Median survival and mortality refer to all-cause mortality.

3.3 All-cause mortality

The basic model (Model 1) pointed to a negative significant association between survival and pet exposure for cat, dog and bird. Once established confounders were introduced in Model 2 all these associations lost their statistical significance and their effects were attenuated. Adjusting for potential mediators (Model 3) further moved the hazard ratio toward the null. In the fully-adjusted model, little changed in terms of significance and magnitude. Moreover, none of the interactions between pets were statistically significant (p-values>0.1, results not shown). Table 3 provides the Cox PH models estimates for all-cause mortality.

Table 3: Cox PH all-cause mortality hazard ratios and 95% confidence intervals for pet exposures, N=23274 , Events=5163

	Model 1		*Model 2*		*Model 3*		*Model 4*	
	HR	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Any pet	1.09***	[1.03-1.16]	1.03	[0.97-1.10]	1.02	[0.96-1.09]	1.04	[0.97-1.11]
Cat	1.07*	[0.99-1.15]	1.01	[0.93-1.09]	1.00	[0.93-1.08]	1.03	[0.95-1.12]
Dog	1.12***	[1.05-1.21]	1.00	[0.93-1.08]	1.00	[0.92-1.08]	1.01	[0.94-1.10]
Bird	1.14**	[1.02-1.27]	1.05	[0.93-1.18]	1.03	[0.91-1.17]	1.05	[0.93-1.19]
Fish	0.91	[0.77-1.08]	0.96	[0.82-1.14]	0.98	[0.83-1.15]	1.00	[0.84-1.19]

Notes: The N and Events of each regression depends on the missing values. *, **, *** denote the significance level at 10%, 5% and 1%, respectively. Model 1 adjusted for age, gender. Model 2 adjusted for Model 1 + education, financial struggle, country, asthma (except for the fish model), depression. Model 3 adjusted for Model 2 + self-perceived health, no. conditions, no. symptoms (+ moderate physical activity, disability for dog only). Model 4 adjusted for Model 3 + household size, marital status, employment status, nursing home, cohort effects, smoking, alcohol consumption, moderate and vigorous physical activity, and BMI.

Stratified analyses were carried using the fully-adjusted model. The only significant association from the gender stratification was that bird exposure in females increased the rate of death by 23%. In this particular case, models 1 through 3 were also examined (results not shown). The basic model yielded the highest magnitude of association ($HR = 1.30[1.12 - 1.51]$), while the total and direct effect models estimated the same hazard ratio ($1.19[1.02-1.40]$). Bird exposure was also statistically significant at the 10% for single-person households, with an additional 27% increase in the rate of death for single household owners, albeit not significant in models 1 through 3. To further test the hazard of bird exposure, we regressed only females who live in single-person households (n=2,964, Events=899) using the fully-adjusted model. This yielded a significant at the 5%, 38% ($CI[1.02 - 1.85]$) higher death rate for those bird owners (estimate shown in Figure 3). Stratified results are presented in Table 4.

Table 4: Stratified all-cause mortality hazard ratios and 95% confidence intervals by gender and household size

	Gender				*Household*			
	Male		*Female*		*Single*		*Multiple*	
	HR	*CI*	*HR*	*CI*	*HR*	*CI*	*HR*	*CI*
Any pet	1.03	[0.94-1.12]	1.06	[0.96-1.16]	1.05	[0.92-1.20]	1.02	[0.95-1.11]
Cat	1.03	[0.92-1.14]	1.04	[0.93-1.16]	1.01	[0.86-1.19]	1.02	[0.93-1.12]
Dog	1.00	[0.89-1.11]	1.04	[0.93-1.17]	0.96	[0.81-1.14]	1.02	[0.93-1.12]
Bird	0.93	[0.79-1.10]	1.23**	[1.04-1.44]	1.28*	[0.98-1.66]	1.00	[0.87-1.15]
Fish	0.97	[0.79-1.20]	1.08	[0.83-1.40]	1.02	[0.65-1.60]	1.00	[0.83-1.20]

Notes: The estimates were obtained using the fully-adjusted model (Model 4). Stratified regressions for any pet had: For males N=10,213, Events=2,583; For females N=11,901, Events=,2229; For single-person households N=4,200, Events=1,335; For multiple-person households N=17,914, Events=3,477 . *, **, *** denote the significance level at 10%, 5% and 1%, respectively.

3.4 Cancer and CVD mortality

The cause-specific models for cancer, CVD and Other mortality, revealed only a significant, at the 10% level, positive association between bird owners and Other mortality ($HR = 1.19[0.97 - 1.48]$). As we had evidence of effect modification by gender, we stratified the model and found that female bird owners are associated with a significant, at the 5% level, increased rate of mortality of other causes ($HR = 1.40[1.05 - 1.88]$) (estimates shown in Figure 3), but not cancer mortality for female cat or bird owners as previous research had suggested (Adhikari et al., 2019, 2020; Buck et al., 2020). Dog or cat ownership was not associated with CVD mortality, in the full and stratified by CVD diagnosis samples, although some vague evidence of a prophylactic relation was there for individuals diagnosed with CVD at baseline ($HR = 0.83[0.66 - 1.04]$)(results not shown). Cause-specific estimates are shown in Table 5.

Table 5: Cause-specific hazard ratios and 95% confidence intervals for pet exposures from the fully-adjusted model

	Cancer		*CVD*		*Other*	
	csHR	*CI*	*csHR*	*CI*	*csHR*	*CI*
Any pet	1.05	[0.93-1.18]	1.00	[0.90-1.12]	0.99	[0.88-1.12]
Cat	1.00	[0.86-1.15]	1.08	[0.95-1.23]	0.96	[0.83-1.12]
Dog	1.09	[0.95-1.25]	0.94	[0.82-1.07]	0.95	[0.82-1.11]
Bird	0.94	[0.75-1.18]	0.99	[0.81-1.21]	1.19*	[0.97-1.48]
Fish	1.13	[0.86-1.49]	0.87	[0.63-1.20]	0.88	[0.63-1.23]

Notes: For the cause-specific model, we use the fully-adjusted model and control additionally for cancer or CVD diagnosis at baseline in the respective model. *, **, *** denote the significance level at 10%, 5% and 1%, respectively.

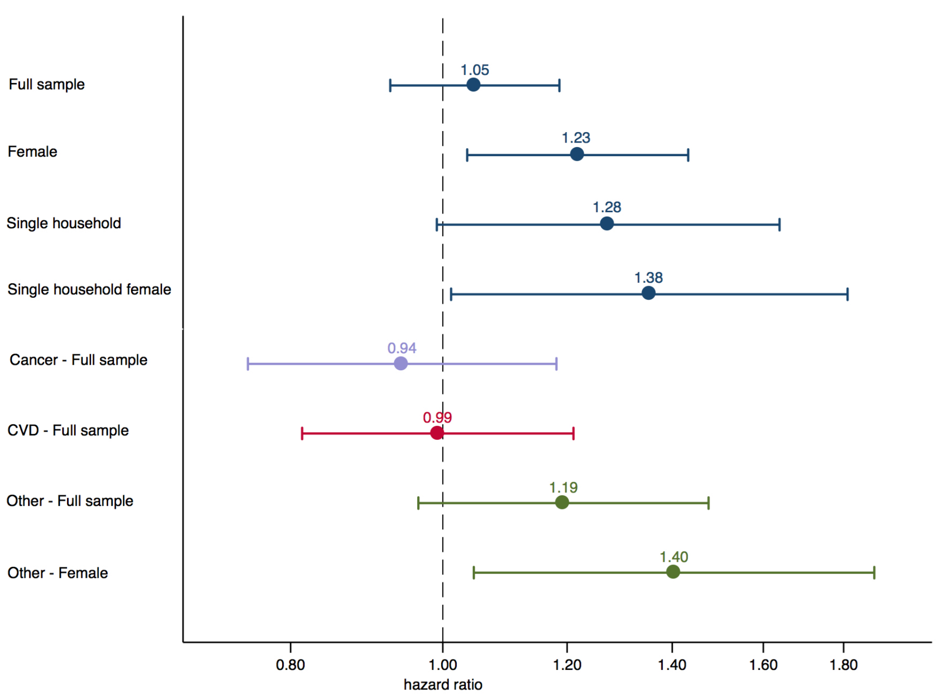

Figure 3: Forrest plot for Bird exposure. Estimates are from the fully-adjusted model. All-cause mortality is shown in blue, cancer in lavender, CVD in red and Other in green. The graph was partially produced using the -coefplot- command (Jann, 2014).

4 Discussion

4.1 Findings in the light of the literature

Overall pet exposure was not associated with survival in this sample of older adults living in Europe. In the disaggregated analysis, cats, dogs and fish did not show any significant associations when we controlled for potential confounders other than age and gender. This was true for cancer, CVD and death from other causes as well. For cats and dogs, this is in accordance with previous research with sufficient controls (Ding et al., 2018; Qureshi et al., 2009; Torske et al., 2017; Gillum and Obisesan, 2010). For fish no previous research exists, to the best of our knowledge, and we did not find something that would spark interest in the research community.

The higher mortality found among female bird owners and/or persons living on their own steers the conversation from lung cancer incidence to perhaps multiple or other causes of death. Although we did not have cancer-specific data to examine the bird-lung cancer relation, our data showed no association with overall cancer mortality in contrast to Buck et al. (2020). But an association was there for causes other than cancer and CVD. This category, among other causes, includes respiratory diseases such as, psittacosis, allergic alveolitis and asthma, diseases long connected with bird exposure (Gorman et al., 2009). We continue with some potential pathogenic mechanisms.

4.2 Potential Mechanisms

The mechanism behind the consistent findings of increased susceptibility of female bird owners remains elusive, although earlier lung-cancer case-control hospital studies that reported adverse effects did include males in their sample and bird breeder's lung (allergic alveolitis) probably took the name from male bird breeders. The fact that we had an amplification effect for single-person households is perhaps evidence of a dose-response, in the sense that single-person households are expected to be smaller in size, hence the air volume and change rate (flow) may be more limited. This signifies increased exposure to allergens and dust particulates such as feather dander, as well as, fomites, excreta and mould (Holst et al., 1988). Chronic inhalation of this bioaerosol might be the main mechanism behind pathogenesis (Holst, 1991). Details of the bird type, number, and location inside the household, will be crucial to further study the matter in an observational setting.

4.3 Missingness & censoring

Pet exposures had less than 0.01% missing values. The variables with the most missing values had less than 2% gaps and concerned education, financial struggle at the household, and BMI. The sample consisted of 22,114 complete cases that represent the 95.02%. A dataset with less than 5% missing values total, is not expected to produce biased estimates in a complete case analysis regardless of the data generating process of the missingness. Nevertheless, pairwise deletion was preferred.

The assumption of independent (right) censoring[20] is crucial for the validity and unbiasedness of the standard TTE analysis results. In medical research, the health status of a participant is the main determinant for attrition, and consequently, right-censoring. This is a big issue when one is studying the treatment effects since more/less healthy individuals systematically remain in the study. Evidence for informative censoring, although uncommon in longitudinal surveys like SHARE, exists due to the not-at-random data generating process caused by attrition, especially when the follow-up is long.

[20]Independent censoring refers to the independence of a persons' censor status from the failure propensity, given a set of factors.

4.4 Modelling & inferential difficulties

Every observational study aims to mimic an experimental design as much as possible. This way, and given that data and methods are robust, results can be given a quasi-causal interpretation.[21] Failing to do so, or even worse not attempting, results in mere associations which are of limited use. Unfortunately, this way of analysis is often preferred and is thought as 'the proper way of data analysis' by a large part of the scientific world. The fear of the word causality and its derivatives is a product of the ideas and works of Karl Pearson that still determine much of the scientific status quo to this day. Despite this hostile environment, causal inference has emerged as a sort of 'new' science, in large part due to the efforts of Judea Pearl and others.

Randomly adding variables to a model is not the way of doing causal inference. The standard practice is to augment models by sequentially adding groups of similar variables such as socioeconomic, lifestyle etc. Although there is a useful interpretation of these model coefficients for the exposure in question, nothing can be said about the total and direct effects. Our analysis focuses on the scientific model that aims to study the effects of a treatment (pet exposure), hence model building follows the principles of causal inference, without the fear of using words banned by editors and the scientific status quo. A fully-adjusted model is provided to fulfil the needs of those who think that there are no bad controls and is used throughout the analysis.[22]

As mentioned earlier in the paper, identifying hard confounders is not easy with pet exposure. Maybe there are no hard confounders since the movement towards the null by adding variables happens so gradually. That is not a problem of course. The main issue is to identify mediators so that the direct effect can be estimated. Since pets are associated with many health outcomes, the direct effect model (model 3) additionally controls for these

[21]Hernán and Robins (2016) refer to this as 'target trial emulation'.

[22]See Cinelli et al. (2020) for an introduction on bad controls.

factors. It is not clear though if the variables weakly influence also the selection of pets, and are therefore, weak confounders. Given that the beginning of the exposure is not known, we have no clear evidence as to whether these variables preceded or succeed pet ownership, and therefore results should be interpreted with caution. Unfortunately, cross-sectional tests on the data are unable to clarify this matter because they cannot rule out the reverse causality scenario, at least most of the times.

4.5 Limitations

Since the questionnaire was not designed to study this particular subject, some limitations regarding the measurement of the exposure are inevitable. The survey does not provide detailed information regarding the human-animal interaction (e.g. the level of attachment to the pet, the duration of the ownership, whether the participant is the actual caretaker), therefore a dose-response effect cannot be estimated. Moreover, the breed is not known, hence further analysis cannot take place. The beginning of the exposure is also unknown, a common drawback of observational studies compared to experimental designs. Consequently, and given that the life expectancy of humans is a lot higher than any of the examined pets, it remains unknown if and when another pet was acquired in the case of a friends' death.

Data from the survey are self-reported. This includes mortality data as well. Both can introduce an amount of measurement error, in particular cause-specific mortality. Despite the surveys' design for random sampling and weights provided, our sub-sample does not allow for these weights to be used, nor can we claim that this is a representative sample of older European residents. Despite this limitation in internal validity, its generalisability remains a lot higher than the rest of the literature since it is the only survival study that pools individuals from different countries. A case can be made for residual confounding, although frailty models did not show the presence of unobserved heterogeneity even in models severely lesser than the fully-adjusted.[23] Nevertheless, rurality is a factor the author wishes he could control for.[24] Finally, mortality is not a measure of quality of life, therefore this study cannot infer whether pet owners live a better life as was previously suggested by Hughes et al. (2020).

The present methodology is not an attempt on mediation analysis and does not aim to estimate the indirect effects. The observed change in the hazard ratios from the two Cox PH models (with and without mediators) does not have a clear causal interpretation and issues can arise with the PH assumption (Wang and Albert, 2017). Nevertheless, it provides indications for mediating or confounding effects of the added variables.

5 Conclusions

No association was evident between pet ownership and survival in this sample of older adults. As similar evidence is accumulating, experimental designs would probably be necessary to challenge and verify the existing literature. Bird ownership, especially among female older adults, requires further investigation with longitudinal studies that include a more comprehensive measurement of the exposure and outcome. Given the existing knowledge, no public health recommendation can be safely made in terms of survival yet.

[23]Gompertz gamma frailty models were used to perform a likelihood ratio test between the frailty and non-frailty model.

[24]The corresponding variable had too many missing values to even consider multiple or another from of imputation.

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A Supplementary material

Table 6: Study sample countries of origin

country	*N*	%
Austria	1,179	5.07
Germany	1,555	6.68
Sweden	2,186	9.39
Netherlands	1,939	8.33
Spain	1,630	7.00
Italy	1,832	7.87
France	1,555	6.68
Denmark	1,326	5.70
Greece	1,781	7.65
Switzerland	1,195	5.13
Belgium	2,305	9.90
Israel	1,932	8.30
Czech Republic	1,107	4.76
Poland	1,247	5.36
Ireland	505	2.17