The science behind "man flu"

Kyle Sue explores whether men are wimps or just immunologically inferior

The term "man flu" is so common that it has been included in the Oxford and Cambridge dictionaries. Oxford defines it as "a cold or similar minor ailment as experienced by a man who is regarded as exaggerating the severity of the symptoms."[1] Since about half of the world's population is male, deeming male viral respiratory symptoms as "exaggerated" without rigorous scientific evidence, could have important implications, including insufficient provision of care.

Despite the universally high incidence and prevalence of viral respiratory illnesses,[2] no scientific review has examined whether "man flu" is appropriately defined or just an ingrained pejorative term with no scientific basis. Tired of being accused of over-reacting, I searched the available evidence (box) to determine whether men really experience worse symptoms and whether this could have any evolutionary basis.

Of mice and men

Mice have long been accepted as good models of human physiology for medical research,[3] with records dating back to William Harvey in 17th century England.[4] Several studies show that female mice have higher immune responses than males.[5 6] This led to the hypothesis that sex dependent hormones have an important role in outcomes of influenza. Further studies suggest that oestradiol is implicated in this response in mice,[7] with one study concluding that the hormone reduces "responses associated with immunopathology" and enhances "responses associated with recruitment of innate immune cells…into the lungs."[8]

However, another mouse study suggests that stress and corticosterone levels have a role, concluding that "the increase in infection-induced corticosterone levels demonstrated in females may have suppressed the behavioural symptoms of infection."[9]

Lending weight to the oestradiol theory, an in-vitro study sniffs at an underlying reason for man flu. Using human nasal epithelial cell cultures infected with seasonal influenza A, researchers showed that exposure to oestradiol or select oestrogen receptor modulators decreased influenza A titres in tissue from female, but not male, donors. Oestradiol also significantly downregulated cell metabolic processes. Adding oestrogen receptor antagonists reversed this antiviral effect.[10]

Another study isolated mononuclear cells from 63 healthy people grouped according to age and sex and cultured the cells with rhinovirus. Cells cultured from premenopausal women had a stronger immune response than those from men of the same age. This difference was not observed when postmenopausal women were compared with men of the same age, suggesting a hormonal link.[11 12]

Patterns in humans

Although animal and in-vitro studies are weak sources of evidence, human research also points to different responses to influenza in men and women. Even the World Health Organization stresses that "sex should be considered when evaluating influenza exposure and outcomes."[13] Epidemiological data from 2004-10 for seasonal influenza in Hong Kong showed that men had a higher risk of hospital admission,[14] and in a US observational study of flu mortality from 1997 to 2007, men had higher rates of flu associated deaths compared with women of the same age. This was true regardless of underlying heart disease, cancer, chronic respiratory system disease, and renal disease.[15]

Studies of influenza vaccination suggest that women are more responsive to vaccination than men.[16 17] This is supported by the finding that women report more local and systemic reactions to influenza vaccine than men in questionnaires.[18] One study noted that men with higher testosterone levels had more down regulation of antibody response to vaccination, suggesting an immunosuppressive role for testosterone.[16] This is consistent with animal and in-vitro studies[19 20] and a finding of higher levels of inflammatory cytokines in men with androgen deficiencies than in healthy controls.[21]

Even the WHO stresses that "sex should be considered when evaluating influenza exposure and outcomes"

The sex differences extend to other respiratory infections beyond influenza. In many acute respiratory diseases, males are more susceptible to complications and exhibit a higher mortality.[22] Wyke and colleagues surveyed men and women consulting general practitioners for common symptoms of minor infectious respiratory illness, finding that "women were significantly more likely to report cutting down activities in response to only one symptom in each cohort."[23] This contradicts the common myth that men cut down activities more than women by exaggerating the severity of symptoms.

Furthermore, in an analysis of retrospective data from a common cold unit on 1700 volunteers inoculated with virus (rhinovirus, coronavirus, influenza, etc) during 1984-89, MacIntyre postulated that "clinical observers are more ready to attribute symptoms and illness to women than to men, and…they under-rate men's symptoms."[24]

Finally, in an unscientific survey completed by 2131 readers of a popular magazine, men reported taking an average of three days to recover from viral respiratory illness compared with 1.5 days for women. The male authors of this study conclude that caregivers should "go that extra mile to care for us when we are stricken with it, so that future shelves can be erected, cars can be maintained and football stadia throughout the land can be well attended"[25]—listing only a few of the many ways male viral respiratory illnesses can affect society.

Immunity gap

Some evidence clearly supports men having higher morbidity and mortality from viral respiratory illness than women because they have a less robust immune system. However, conclusions may be limited by author bias, inclusion of some low level evidence, and not reporting a critical appraisal of the studies cited. Additionally, the differences observed in these studies may not be representative of all respiratory viruses, and differences may be hidden within studies that did not stratify the various viruses or other differences between the sexes.

The sex difference in immunity has been suggested to be modulated by hormonal differences, with oestradiol being immunoprotective and testosterone being immunosuppressive. However, the reviewed studies did not consider other differences between the sexes—for example, men have higher rates of smoking worldwide[26] and are less likely to take preventive care or seek care when ill.[27] Hormonal influence on immune response is supported by evidence that pregnant women have more severe influenza symptoms and reduced symptoms from autoimmune diseases than non-pregnant women.[28 29] However, it is unclear how this is mediated or might apply to a difference between the sexes, given the changes in oestrogen, progesterone, and other hormones along with other stressors that occur during pregnancy.

If the differences found in the above studies are real, the evolutionary purpose of men's higher symptoms from viral respiratory infections remains unclear. Zuk postulates that "if males require, for example, testosterone for aggressive behaviour and the development of male secondary sexual characteristics, selection for winning at the high-stakes game males play may override the cost of any immunosuppressive effects of the hormone."[30] Likewise, the authors of another study speculate that reduced immunity is less important for men because males of many species are more likely to die from trauma before an infection kills them.[16] Other academics agree that across species, the male strategy of "live hard, die young" arising from stronger intra-sexual competition than among females has led to less investment in immunity[31] and that "mounting immune responses

METHODS

I searched PubMed/MedLine, EMBASE, Cochrane, CINAHL, Web of Science, Scopus, and Google Scholar using combinations and variants of terms "man"/"male", "woman"/"female", "gender"/"sex", "influenza"/"flu", "viral", "respiratory", "common cold", "difference", "comparison", "intensive care." I read the abstracts of all articles found and narrowed articles down by relevance. References in each article were then hand searched to ensure comprehensiveness

to clear viruses requires metabolic resources that might otherwise be used for other biological processes, such as growth, maintenance of secondary sex characteristics, and reproduction."[32]

Avitsur and colleagues suggest the increase in male sickness may be a strategy important for survival since "it promotes energy conservation and reduces the risk of encountering predators."[9] Classic modes of energy conservation may include lying on the couch, staying in bed, or receiving help with basic activities, which could all be effective predator avoidance tactics.

Further higher quality research is needed to clarify other aspects of man flu. It remains uncertain whether viral titres, immune response, symptoms, and recovery time can be affected by environmental conditions. An example of future research may include a controlled trial in which men are infected with a respiratory virus, then subjected to rigorous research conditions in which all their requests are met by a healthy caregiver or they are left to fend for themselves. Another potential study may examine whether men with robust immune systems are less successful at mating compared with those with weaker immune systems and correspondingly higher testosterone. In other words, can the blame for man flu be shifted to the people who select these men as sexual partners rather than the men themselves?

Time to rest

The concept of man flu, as commonly defined, is potentially unjust. Men may not be exaggerating symptoms but have weaker immune responses to viral respiratory viruses, leading to greater morbidity and mortality than seen in women. There are benefits to energy conservation when ill. Lying on the couch, not getting out of bed, or receiving assistance with activities of daily living could also be evolutionarily behaviours that protect against predators. Perhaps now is the time for male friendly spaces, equipped with enormous televisions and reclining chairs, to be set up where men can recover from the debilitating effects of man flu in safety and comfort.

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Does Peppa Pig encourage inappropriate use of primary care resources?

As a general practitioner, says **Catherine Bell**, I have often wondered why some patients immediately attempt to consult their GP about minor ailments of short duration. As the mother of a toddler and frequent witness to the popular porcine children's television series, I might have discovered the answer

The TV show *Peppa Pig* centres around a young pig, Peppa, her family (brother George, Mummy Pig, Daddy Pig), and animal friends and members of the community.

Dr Brown Bear, a single handed GP with whom the Pig family is registered, appears to provide his patients with an excellent service—prompt and direct telephone access, continuity of care, extended hours, and a low threshold for home visits. But could this depiction of general practice be contributing to unrealistic expectations of primary care? In this article, I present three case studies and consider the potential impact Dr Brown Bear's actions could have on patient behaviour.

Discussion

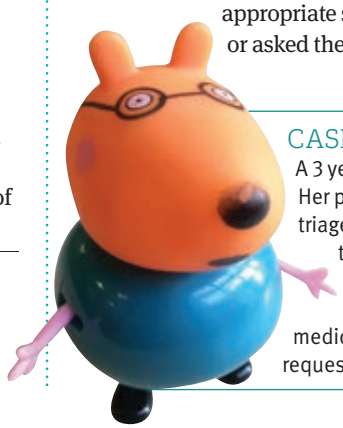
Given that *Peppa Pig* is broadcast and encountered by parents in more than 180 countries worldwide, the influence of his portrayal of the work of primary care physicians is likely to be significant.

Case 1 questions whether Dr Brown Bear is an unscrupulous private practitioner, rather than an NHS GP.[1] In this case of a probable viral rash, he could reasonably have encouraged self management (with appropriate safety netting) or asked the family to attend surgery for assessment. His decision not to suggests a potential financial incentive for conducting an arguably clinically inappropriate home visit.

Case 1 is also an example of unnecessary prescribing for a viral illness, and encourages patients to attempt to access their GP inappropriately. Depending on interpretation of the medicine, Dr Brown Bear is either prescribing antibiotics in an era of rising antibiotic resistance, or is issuing on prescription medication (paracetamol?) that is available over the counter. In the context of the UK's NHS, this creates a potential drain on resources.

In **Case 2,** Dr Brown Bear conducts a telephone triage outside normal working hours and again opts to make a clinically inappropriate urgent home visit. Had he explored Daddy Pig's ideas, concerns, and expectations, he would have discovered that Daddy Pig already had a good understanding of the likely diagnosis and self limiting nature of the illness. However, Dr Brown Bear's management was at least clinically appropriate on this occasion, and his advice might encourage the family to self manage similar illnesses in future.

By **Case 3,** Dr Brown Bear displays signs of "burnout." His disregard for



CASE STUDY 1: **NOT VERY WELL**

A 3 year old piglet develops an erythematous maculopapular facial rash. Her parents call Dr Brown Bear, who operates a "doctor first" telephone triage system. Dr Brown Bear advises putting the patient to bed and opts to make an urgent home visit.

He examines the patient's tongue, diagnoses a "rash," and reassures the parents it is "nothing serious." He offers a dose of medicine, despite admitting this is purely in response to the patient's request, and says the rash is likely to clear up quickly regardless.

RICHARD H SMITH

CASE STUDY 2: **GEORGE CATCHES A COLD**

Parents call Dr Brown Bear on a Saturday regarding an 18 month old piglet with a 2 minute history of coryzal symptoms after playing outside without his rain hat.

Dr Brown Bear telephone triages and makes an urgent home visit.

After examining the throat, he diagnoses an upper respiratory tract infection and advises bed rest and warm milk. Symptoms resolve within 12 hours.

confidentiality, parental consent, record keeping, and his self prescribing indicate that the burden of demand from his patient population is affecting his health. He is no longer able to offer the level of service his patients have come to expect.[2]

Dr Brown Bear's prescription policy creates a potential drain on scarce NHS resources

Conclusion

Peppa Pig conveys many positive public health messages, encouraging healthy eating, exercise, and road safety.[3] However, from (repeated, mostly involuntary) review of the subject material, I hypothesise that exposure to *Peppa Pig* and its portrayal of general practice raises patient expectation and encourages inappropriate use of primary care services. Further study is needed to confirm this.[4]

Dr Brown Bear was approached for his perspective on the cases discussed; however, he is unable to comment pending the outcome of a fitness to practise investigation.

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Conflicts of interest: None declared. It may look like my child is sponsored by *Peppa Pig*, but any claims to this effect are false.

[1] Despite being a UK resident with access to the NHS, it is possible that Daddy Pig holds private health insurance through his employer—readers well versed in *Peppa Pig* will be aware he works as a structural engineer, whereas Mummy Pig writes nonsense letters on her computer from home for no obvious reason. They both, however, appear to be regularly available to drop off and collect their children from playgroup without any additional childcare. Further study is needed to ascertain how this is achieved.

[2] Another contributing factor to Dr Brown Bear's exhaustion is likely to be that he also provides medical cover for a community rehabilitation ward (Series 3: *Hospital*).

[3] To quote Mr Potato in *Fruit*, Series 4: "Apple, orange, banana, pear, and pineapple too; Eat five pieces of fruit a day, because they're good for you!"

CASE STUDY 3: **PEDRO'S COUGH**

A 3 year old pony coughs three times while attending playgroup. The nursery teacher immediately calls Dr Brown Bear, who telephone triages and makes an urgent visit to the playgroup. In a green light car. With sirens.

Dr Brown Bear takes a focused history, asking if it is "a tickly cough or a chesty cough?" and inquires about duration of symptoms. He does not commit aloud to a diagnosis, but administers a dose of medicine immediately and warns that the cough is potentially transmissible.

The rest of the playgroup attendees and their parents become symptomatic, and all are given a dose of an unspecified pink medicine.

Dr Brown Bear also quickly becomes symptomatic. His patients attend the surgery to administer his dose of medicine, and to sing to him.

[4] Recruitment of a cohort of control patients without prior exposure to the subject material has proved difficult.

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ORIGINAL RESEARCH Population based cohort study

Associations of pet ownership with biomarkers of ageing

G David Batty, Paola Zaninotto, Richard G Watt, Steven Bell

Objective To examine the prospective relation between animal companionship and biomarkers of ageing in older people.

Design Analyses of data from the English Longitudinal Study of Ageing, an ongoing, open, prospective cohort study initiated in 2002-03.

Setting Nationally representative study from England.

Participants 8785 adults (55% women) with a mean age of 67 years (SD 9) at pet ownership assessment in 2010-11 (wave 5).

Main outcome measure Established biomarkers of ageing in the domains of physical, immunological, and psychological function, as assessed in 2012-13 (wave 6).

Results One third of study members reported pet ownership: 1619 (18%) owned a dog, 1077 (12%) a cat, and 274 (3%) another animal. After adjustment for a range of covariates, there was no evidence of a clear association of any type of pet ownership with walking speed, lung function, chair rise time, grip strength, leg raises, balance, three markers of systemic inflammation, memory, or depressive symptoms.

Conclusion In this population of older adults, the companionship of creatures great and small seems to essentially confer no relation with standard ageing phenotypes.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

- Half of older people in the UK own a pet and 12% of older Australians report that animals are their predominant form of companionship
- The relation of animal companionship, a potentially modifiable characteristic, with biomarkers of ageing in older people is largely unknown

WHAT THIS STUDY ADDS

- Of 11 biomarkers of ageing, there was no evidence of a clear relation with pet ownership

Introduction

The notion that animal companionship might be linked to human health, particularly cardiovascular events, has a long research pedigree.[1] That 12% of older adults in Australia report that a pet is their predominant form of company[14] raises the importance of assessing the link, if any, between this behaviour and functional capacity in this group. Accordingly, using prospectively gathered data, we examined the association between pet ownership and a range of biomarkers in older people.

Methods

The English Longitudinal Study of Ageing (ELSA) is an ongoing, open, prospective cohort study of a representative sample of men and women who were aged 50 or more when recruited and living in private households in England (2002-03).[18] Data have been collected biennially, with biomedical assessments during alternate waves. For the purposes of our analyses, the study baseline is from wave 5 (2010-11) when pet inquiries were first introduced.

Biomarkers

Physical—Biomarkers of ageing were collected in the home at wave 6 (2012-13), around two years after assessment of pet ownership.[20] A walking speed test (2.4 m and back) was administered to those aged 60 or more.[21] Measures of physical strength included hand grip and the timed chair stand test.[22] Static balance was evaluated in three separate and progressively more difficult tests[3 24]: side-by-side and semi-tandem stand (each scored 1 if held for 10 seconds) and full tandem stand (scored 1 if held for 3-10 seconds, 2 if held for longer). A total score of 3 or less denoted impaired balance.[23] A leg raise assessment was administered to those aged less than 70 years who successfully completed the side-by-side balance test: with their eyes open, study members were asked to raise one leg for 30 seconds from a standing position. Forced expiratory volume in one second was ascertained using a standard spirometer.[25]

Immunological—Blood samples were analysed for inflammatory markers, including acute phase reactants (high sensitivity C reactive protein, white blood cell count) and coagulation products (fibrinogen).[26 27]

Psychological—Memory was measured with a word list learning test: participants were asked to recall 10 words immediately after reading, and after a five minute delay.[29 30] Scores on both tests were totalled (range 0–20). Depressive symptoms were assessed at baseline and follow-up using the eight item Centre of Epidemiological Studies Depression scale[31] (we used a score of ≥3 to define "caseness").[32 33]

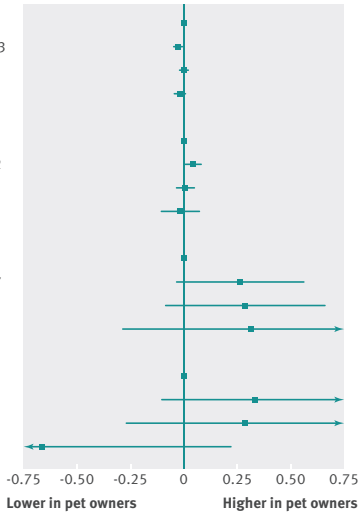
Collateral data

Height and weight were measured using standard procedures and body mass index was computed using the conventional formula.[23 34] The remaining data were self-reported. Cigarette smoking was classified as current, former, or never. An assessment of physical activity was based on items about engagement in vigorous, moderate, or mild intensity activities (5 point scale, with lower values denoting more sedentary behaviour). Alcohol intake was based on units consumed weekly.[35] Our socioeconomic variable was total net non-pension household wealth as based on an estimation of the assets of study members and their partners.[36 37] We created an index of social isolation from responses to questions about marital status/cohabitation, contact with family or friends, and participation in social groups.[38] A higher score indicating less social contact. Degree of loneliness was ascertained using an established loneliness scale (revised)[39]; a higher score reflecting higher levels. Participants were also asked to rate their health on a 5 point scale. In post hoc analyses, we also controlled for baseline measurement of the outcome of interest at wave 4 (2008-09).

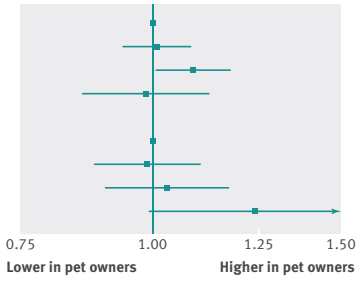
Statistical analyses

We imputed missing data and log transformed the inflammatory markers data as these were not normally distributed.[41] β

Part A	Age and sex adjusted β (95% CI)	P value	Multivariable adjusted β (95% CI)	P value
Gait speed (m/s)				
No pet	0 (reference)		0 (reference)	
🐶	-0.03 (-0.05 to -0.02)	<0.001	-0.02 (-0.04 to -0.01)	0.003
🐱	≈0.00 (-0.02 to 0.02)	0.7	≈0.00 (-0.02 to 0.01)	0.8
Other pet	-0.04 (-0.08 to -0.00)	0.04	-0.02 (-0.06 to 0.02)	0.3
FEV1 (L/s)				
No pet	0 (reference)		0 (reference)	
🐶	≈0.00 (-0.04 to 0.04)	0.9	0.04 (0.01 to 0.08)	0.02
🐱	0.01 (-0.03 to 0.05)	0.7	0.01 (-0.03 to 0.05)	0.6
Other pet	-0.06 (-0.14 to 0.03)	0.2	-0.01 (-0.09 to 0.07)	0.7
Chair rise (s)				
No pet	0 (reference)		0 (reference)	
🐶	0.58 (0.26 to 0.90)	<0.001	0.27 (-0.03 to 0.56)	0.07
🐱	0.25 (-0.13 to 0.63)	0.2	0.30 (-0.06 to 0.66)	0.1
Other pet	0.75 (0.10 to 1.39)	0.02	0.32 (-0.28 to 0.92)	0.3
Grip strength (kg)				
No pet	0 (reference)		0 (reference)	
🐶	0.04 (-0.40 to 0.48)	0.9	0.33 (-0.09 to 0.75)	0.1
🐱	0.43 (-0.14 to 0.99)	0.1	0.29 (-0.25 to 0.83)	0.3
Other pet	-1.08 (-2.00 to -0.16)	0.02	-0.67 (-1.55 to 0.22)	0.1



Part B	Age and sex adjusted RR (95% CI)	P value	Multivariable adjusted RR (95% CI)	P value
Leg raise failure				
No pet	1 (reference)		1 (reference)	
🐶	1.05 (0.97 to 1.13)	0.2	1.00 (0.93 to 1.08)	0.9
🐱	1.08 (1.00 to 1.16)	0.1	1.09 (1.01 to 1.17)	0.03
Other pet	1.04 (0.90 to 1.21)	0.6	0.98 (0.85 to 1.13)	0.8
Balance failure				
No pet	1 (reference)		1 (reference)	
🐶	1.07 (0.96 to 1.19)	0.3	0.98 (0.88 to 1.10)	0.8
🐱	1.01 (0.88 to 1.15)	0.9	1.03 (0.90 to 1.17)	0.7
Other pet	1.39 (1.11 to 1.75)	0.004	1.24 (0.99 to 1.55)	0.1



β coefficients (top panel) and relative risks (bottom panel) for relation of pet ownership with ageing biomarkers: physical functioning (n=8785). Multivariable adjustment is for age, sex, wealth, isolation, loneliness, self- ated health, physical activity, cigarette smoking, alcohol intake, and body mass index

coefficients (95% confidence intervals) were estimated using a series of linear regression models; for the log transformed data, these coefficients and confidence intervals were multiplied by 100 and expressed as percentages.[42] We used modified Poisson regression[43] to estimate relative risks for binary outcomes. We adopted a Bonferroni corrected P value threshold of < 0.0045 (0.05÷11 outcomes) as providing strong evidence of differences in biomarkers between the pet ownership groups.

Results

After imputation, in our analytical sample of 8785 (4863 women) the mean age at baseline was 67 (SD 9) years (see fig 1 and table 1 on bmj.com). About one third of study members reported owning any type of animal: 1619 (18%) a dog, 1077 (12%) a cat, and 274 (3%) other.

After adjustment for multiple covariates, there were no strong relations between different types of pet ownership and various physical biomarkers of ageing, and statistical significance at conventional levels was rarely apparent. Compared with participants who did not report pet ownership, dog companionship was associated with slower walking speed and a longer time to rise from a chair, but slightly higher pulmonary function (fig 2). Cat owners were more likely to fail the leg raise test. Pet ownership was essentially unrelated to the immunological markers investigated (see fig 4 on bmj.com). There was also no apparent relation between ownership of any type of pet and cognitive function or depressive symptoms (see fig 5 on bmj.com).

Discussion

Of the widely used biomarkers of ageing we prospectively related to pet ownership in this study, there was no clear evidence of strong associations. Some possible exceptions were walking speed and chair rise time; both less favourable among dog owners,

Dog companionship was associated with slower walking speed and a longer time to rise from a chair

although the magnitude of these effects was again low.

The present study has some strengths, which include its size; the prospective analyses of the relation between pet ownership and health, which reduces concerns about reverse causality; and the range of covariates captured, which allowed us to explore alternative explanations for the investigated associations.

Limitations of the study were that pet ownership was only measured on one occasion, and with evidence suggesting that this characteristic is time varying,[44] repeat assessment would provide more accuracy. It is likely, however, that this variation over time in pet ownership would lead to an underestimation of the true effects.[45] Second, it may be that pet ownership has an impact on health outcomes not included in our analyses, such as biomarkers of psychological stress. Third, we had no information on who was responsible for the care of the pet. We also did not have specific details of ownership which, in addition to caretaking, include frequency of interaction, age of the animal, duration of ownership, and, in the case of dogs, time spent walking.[46] Finally, as our study was observational, we cannot of course exclude residual confounding.

Conclusion

In the present study, the companionship of creatures great and small seems to confer essentially no relation with standard physical and psychological biomarkers of ageing.

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