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Title: Interactions between caregiving and sex and the antibody response to COVID-19 vaccination

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Abstract

Objective: Antibody response to vaccination is a powerful paradigm for studying the effects of chronic stress on immune function. In the present study, we used this paradigm to examine the interaction between caregiving (as a type of chronic stress) and sex on the antibody response to a single dose of a COVID-19 vaccination; recent research has called for examination of sex differences on health outcomes among family caregivers. A three-way interaction between caregiving, sex and psychological distress was also examined.

Methods: COVID-19 antibody data was extracted from 165 caregivers (98 females) and 386 non-caregivers (244 females) from the UK's Understanding Society COVID-19 study. Relevant socio-demographics, health and lifestyle, and distress variables were gathered as potential covariates.

Results: In a 2 x 2 ANOVA we found the interaction between caregiving and sex was significant; male caregivers had a lower antibody response to the vaccine compared to female caregivers F (1,547), =24.82, p <.001, η^2 = .043. Following adjustment, male caregivers had the lowest antibody response relative to all other groups. The three-way interaction model, controlling for covariates was also significant, $R^{2 =}$ .013, p = .049; the conditional effects for the three-way interaction revealed that male caregivers, compared to the other groups had a lower antibody response at both low and medium levels of psychological distress.

Conclusion: This study found evidence of a three-way interaction between caregiving, sex and distress on antibody response. Male caregivers had poorer antibody response to a single shot of the COVID-19 vaccination than female caregivers and male and female non-caregivers and this was evident at low and medium levels of distress. Our findings will be discussed in relation to the caregiver-and sex interactions during the pandemic.

Keywords: Antibody response; Caregiving; COVID-19; Gender; Psychological Distress; Sex

1. Introduction

Informal family caregiving, i.e., caring for a sick or disabled relative or friend, is a well-established model for examining the effects of chronic stress on immunity (1-3). To date, this work has confirmed in most cases, but not all (4, 5), that caregivers tend to have higher levels of inflammation (6), allostatic load (7), accelerated immunological aging (8) and poorer adaptive immunity (9). One aspect of adaptive immunity, the specialised and targeted arm of the immune system, that is influenced by caregiving is antibody response to vaccination. For example, studies have found that older spousal caregivers of people with dementia have a lower antibody response to both viral, i.e., thymus-dependent (10) and bacterial vaccines, i.e., thymus-independent (11), and similar effects have been observed for younger carers, i.e. parents caring for children with disabilities (12, 13). Thymus-dependent vaccines are where the immunogens can stimulate B cells to make antibodies with help from T cells (as in the case of thymus-dependent antigens) whereas thymus-independent vaccines do not require T cell help (14). Although the negative effects of 'age' on antibody responses are well-established (15, 16), it seems from the studies above that where the stress of caregiving is reported to be high, younger and older caregivers are both affected, implying that other caregiving factors and not immunesenescence *per se* is what matters for caregiver health. However, another demographic factor, which also significantly influences antibody response but is often overlooked in this context is sex/gender. This is despite studies demonstrating differences among male and female caregivers on health outcomes (17). As such, this will be the focus of the present study.

It is important to examine the impact of sex in this context because as a biological variable it has been found to be associated with immunological responses including antibody response to vaccination (18, 19); generally, females tend to have a higher vaccine efficacy compared to males. While sex refers to the biological, gender reflects the behavioural and societal activities shaped by culture, and both have been found to influence immune responses (18). Historically, caregiving is heavily gendered, with women more likely to take on these caring roles, give up work, and take on more personal caring tasks (20-23). This inequity of care is a likely consequence of the socialization of gender roles where there are norms and cultural expectations around women taking on the family caring role contrasting with men as providers. However, contemporary caregiver research has found that the proportion of men who provide care has been increasing (24). Moreover, in terms of health and sex differences

among caregivers, two systematic reviews have found that females tend to report higher caregiver burden, depression and have poorer health relative to males (17, 24), albeit these effects were noted to be small. While females are more likely to be caregivers and report poorer health, it is not unusual to find the opposite, with male caregivers of people with dementia reporting greater negative affect compared to their female counterparts (25). In addition, one recent longitudinal study from the Netherlands found that women, compared to men, were more likely to have stopped and reduced caregiving duties during the pandemic and that caregiver burden decreased in women and increased in men so that it was more equally distributed among men and women (26). Another study looking at the effect of caregiving during COVID-19 from the United States, found that among parental caregivers, fathers were more likely to report higher stress and depression compared to mothers (27).

From a biological perspective, female caregivers had lower numbers of T-helper cells and fewer natural kill cells than males (28). However, in the Whitehall II cohort study, informal male caregivers but not female caregivers displayed a blunted cortisol awakening response (29), implying a negative effect of caring on this stress hormone. In addition, elevated levels of D-dimer and inflammatory cytokine IL-6 have been found in male caregivers relative to females (30). Other work has also suggested that male caregivers may be more immunologically vulnerable with lowered CD4 counts in comparison to male controls, with caregiving men displaying alterations in lymphocyte beta-receptor sensitivity (31). Despite this, a recent meta-analysis has noted that few studies have specifically examined sex effects, with the majority not accounting for potential confounds, highlighting the need for further research to examine any sex-specific effects of caregiving and health (17). In fact, in the context of caregiving and the antibody response to vaccination, few studies have examined sex effects (4, 10, 12, 13, 32, 33), supporting the rationale for seeking further clarity on sex differences in antibody responses among caregivers.

In this study, we examined the antibody response to a single shot of COVID-19, i.e., thymus-dependent vaccine, which has been recently shown to be influenced by psychosocial stress (34). The analysis of the single shot is an indicator of a primary immune response, which allows us to investigate the response mounted to the novel antigen, i.e., SARS-Co-V2. Further, a recent review has found that females tend to have a higher response to the COVID-19 vaccines (35), while another study showed that the sex/gender differences in mortality from COVID-19 varied not necessarily by biological factors but rather by socio-contextual and behavioural factors (36). Given the importance of socio-contextual factors for explaining

antibody response variation we included a measure of psychological distress as this may provide some insights into the psychosocial pathways behind any observation. Recent research has found that female caregivers reported higher levels of psychological distress during the COVID-19 compared to their male counterparts (37, 38). In addition, psychological distress has been found to influence antibody responses to vaccination(39) including the COVID-19 vaccine (40). Taken together, and based on the above research, this study aims to examine the interaction between sex and caregiving on the antibody response to vaccination. We hypothesise that female caregivers would have a lower antibody response compared to male caregivers and non-caregivers. In addition, exploratory analysis also tested the three-way interaction among gender, caregiving, and distress.

2. Methods

2.1. Study design and participants

Participant data was extracted from two waves (January 2021 and March 2021) of the *Understanding Society* UK Household Longitudinal Study (UKHLS) COVID-19 study (41). The Understanding Society is a large population level study (around 40,000 UK households) that started in 2009 with data collected every two years and it explores how life in the UK is changing from a social, economic, behavioural and health perspective. The data is freely available from the UK Data Service and during the COVID-19 pandemic they instigated an online survey rather than face-to-face as had been previously. For our analysis we used this COVID-19 dataset, and we needed a sample size of 351, this was based on two groups, 6 covariates, and a power of .80, and an effect size of .15. Socio-demographics and health behaviour data were extracted from the January 2021 dataset as these are likely confounders (42). In January of 2021 participants were asked if they would provide a blood sample for detection of COVID-19 antibodies, and in March 2021, 6,600 participants provided a blood sample to detect COVID-19 antibodies in response to natural infection or vaccination. This March survey also asked if they had COVID-19, and if they had the vaccination; here we focus on vaccination data only. After sample weighting and excluding those not receiving a vaccine, we were left with a sample of 552 (See Table 1) who reported receiving a single shot of a COVID-19 vaccine and who did not report a prior infection. This prior infection would indicate a secondary immune response (14) and as such was not the focus of the current study. Caregiving status was ascertained in the March survey only from the questions: “Is there anyone in your own home who is sick, disabled or elderly whom you look after or give special help to” which had a Yes/No format. A similar question was asked for those caring

outside the home; those answering Yes to both were pooled together to create a single caregiver group; see Table 1 for socio-demographic characteristics of both caregivers and controls. As an index of caregiver burden, caregivers were also asked how many hours they care per week, ranging from 1= 0-4 hours, 2 =5-9 hours, 3 =10-19 hours, 4 = 20-34 hours and 5= 35-49 hours, 6 =50-99+ hours). Sex was ascertained by endorsing male, female or prefer not to say. The latter category was endorsed in our sample. All participants gave informed consent and ethical approval was obtained by the University of Essex, UK from NHS Health Research Authority, London – City & East Research Ethics Committee, reference: 21/HRA/0644.

2.2. Psychological Distress

Distress was measured by the 12-item General Health Questionnaire (GHQ) (43) in the January 2021 survey only. These items (e.g., lost sleep over worry, losing confidence in self) assess the severity of depressive symptoms over the past few weeks using a 4-point scale (from 0 to 3). This generated a total score ranging from 0 to 36, with higher scores indicating higher symptoms. The scale has been previously used to capture psychological distress in caregivers (44) and an excellent Cronbach's alpha (.89) was observed here.

2.3. Covariates

From the January 2021 dataset, we were able to consider the influence of participants reporting a chronic health condition (yes/no), and health behaviours including smoking (yes/no), portions of fruit/veg intake per day and alcohol taken in the previous month, 1= yes, and 2 = no. The number of days walking for 30 minutes or more per week was also included. These are potential confounding factors and accounting for these is in line with other vaccine studies and theoretical papers (12, 14, 45, 46).

2.4. Vaccine, Blood Sampling and Antibody Analysis

Although there was no data available in the dataset as to what make of vaccine was used, we do know the Pfizer vaccine was administered in the UK just before January 2021, and it was the Oxford/AstraZeneca vaccine was the main vaccine given after this period and for this particular age group (see age group in Table 1). The main period covered for this vaccine administration was from January 2021 onwards as such it is most likely to be a primary vaccination as the follow-up was 4-12 weeks period. For antibody assessment, participants

received via post a labelled home COVID-19 testing kit (via Royal Mail); an information sheet and a link to a YouTube video on how to collect the blood sample (0.5ml) was also provided. They were instructed to take a finger prick blood sample as soon as possible, i.e. within a few days (1-week max) and these were returned to the laboratory, *Thriva*, (https://thriva.co/). While there was no detail provided in the dataset on the assays employed for detection of COVID-19 specific antibodies, the sampling kit insert which is available from the *Thriva* website notes that the assay uses a recombinant protein representing the nucleocapsid antigen in a double-antigen sandwich assay for detection of the IgG spike protein. A value of 0.8 U/ml needed for a positive vaccination response. Thus, the final sample for the primary antibody response outcome was $N = 551$ (165 caregivers).

2.5. Data reduction and analysis

Our analysis was conducted using version 27 of the Statistical Package for Social Sciences (SPSS; IBM). Following sample weighting for the UKHLS COVID-19 (see (47) for weighting details and checking for data skewness), antibody titers were skewed and therefore subjected to $\log_{10}$ transformation for parametric testing. Sample weights were applied to allow more accurate population estimates and to ensure that hard to reach groups like family caregivers are represented. Initial analyses focused on descriptive statistics, and tests of differences, including F-tests for interval and chi-squared for nominal data, across the socio-demographic, health, and lifestyle variables and distress measure. Analyses then focused on the main hypotheses, and a 2×2 (caregiver group x sex) analysis of covariance (ANCOVA) was conducted on $\log_{10}$ antibody response, with potential confounders (e.g. age, relationship status, ethnicity and smoking) as covariates. Where appropriate, post-hoc tests were undertaken using simple effect tests. A similar set of analyses was undertaken on the distress measure. To model the three-way interaction between caregiving, sex and distress on antibody response we used PROCESS model 2 (48) to examine the interaction and for these we also accounted for the above covariates. Partial eta-squared (η^2_p) was reported as a measure of effect size. Minor variations in degrees of freedom reflect missing data on some variables.

3. Results

3.1 Sample characteristics and descriptive statistics

As can be seen in Table 1, caregivers and controls were similar on age, relationship status, ethnicity, annual income and health status. However, there were more females in the caregiver groups, and caregivers were more likely to be smokers and reported higher levels of distress relative than non-caregiver controls, η^2_p = .014 effect size. There were no other differences on health behaviours. In Table 2, we report sex differences and as can be seen, males were older, more likely to be living with a partner and non-white but also be a smoker and reported less psychological distress. Given these sex differences we controlled for these factors in our main analyses. Further, there were no differences among our male (4.6 $\pm$ 2.14) and female (4.5 $\pm$ 1.96) caregivers on hours caring, p =.73.

[Insert Table 1 About Here]

3.2 Antibody Response

In a 2x2 (caregiver group x sex) factorial ANCOVA, controlling for smoking status, there was no main effect of caregiver status, F (1,550) = 1.97, p = .18, η^2_p = .003 on antibody response. However, there was a main effect for sex, F (1,550) = 24.28, p <.001, η^2_p = .043), In addition, the interaction between caregiver status and sex was significant, F (3,544) = 9.58, p = .002, η^2_p =.017); here, following simple effect analysis with Bonferroni correction there were no sex differences between male and female non-caregivers. However, male caregivers had a lower antibody response compared to female caregivers, and both male and female non-caregivers. We re-ran this analysis, controlling for sex differences on age, relationships status, ethnicity, smoking status, and distress our results above remained unchanged, F (8,545) = 7.91, p = .005, η^2_p =.014).

3.3. *Three-way interaction*

We tested if there was a caregiver, sex and psychological distress interaction on antibody response using Process (model 2). In this analysis, caregiver status was significant, b = -.51, t= -2.347, p = .019, 95% CI [-.93, -.08], as was the sex effect, b = .11, t= 1.986, p =.047, 95% CI [.001, .22]. We also confirmed the two-way interaction by caregiver X sex found above, $R^{2=}$.010, p = .032, but not the caregiver X distress interaction, $R^{2=}$.002, p = .271. However, the three-way interaction was significant, $R^{2=}$.013, p = .049. Further, conditional effects showed that a lower antibody response was found for male caregivers compared to male-non-carers at both low and moderate (the mean) levels of distress and for female carers and female non-carers at all distress levels, b = -.22, t= -2.12, p = .032, 95% CI [-.42, -.02] (See Figure 1).

[Insert Figure 1 About Here]

4. Discussion

To our knowledge, this is the first study to demonstrate that male caregivers have a poorer antibody response to vaccination compared to their female counterparts and male and female non-caregivers. In addition, when we factored levels of psychological distress into this equation and examined the interactions, male caregivers who reported low and mean levels of psychological distress had the lowest antibody response relative to the other groups. Moreover, these effects were robust enough to withstand adjustment for several potential confounding factors (e.g. relationships status, ethnicity, and smoking). Taken together, our study suggests that the effects of sex on the caregiver-health relationship are worthy of investigation and that male caregivers, especially in the context of immunity and the COVID-19 pandemic were more vulnerable.

Our study is consistent with several other studies that have examined the influence of antibody response to several vaccination types, including exposure to novel antigens as well as primary and secondary immune responses to these vaccines (14, 49-51). It also supports the recent theoretical paper suggesting that these factors may hold relevance for the antibody response to COVID-19 vaccines (52). In fact, a recent study demonstrated that more group based social factors are influential for antibody response to these vaccines (34), but here we show it at a more individual level. More specifically, our caregiver findings are also consistent with several other studies that have found a poorer response among caregivers. For example, a lower response to a thymus-independent bacterial vaccine (e.g., pneumococcal) was found in older spousal caregivers of dementia patients relative to controls (11). A similar pattern of results has been found for thymus-dependent vaccines (e.g., influenza) (10). Elsewhere this negative impact of caregiving on antibody response to both vaccine types simultaneously has also been demonstrated in a younger sample of family caregivers (12, 13). However, here we extend on these studies, and demonstrate this effect is more evident in male caregivers, and for a novel antigen vaccine, the COVID-19 vaccination. In terms of implications, given the ongoing public health impact of the virus and the emergence of other COVID-19 strains the implications become clear; those with lower antibody levels have been found to have poorer clinical outcomes and more severe disease (53). Moreover, we have shown that beyond well-established predictive factors such as age, health conditions, and

other contextual factors such as the interactions between chronic (di)stress and sex do matter (46, 54).

Importantly, in trying to understand why male caregivers are more vulnerable from a biological perspective, sex hormones, in particular estrogen, are thought to underlie the higher antibody response in females (19) due to increasing levels of circulating antibodies potentially through anti-inflammatory signaling pathways and also the regulation of T-helper cells (Harding & Heaton, 2022). In contrast, testosterone is thought be associated with lower antibody responses to the influenza vaccine in men (55) but the evidence is mixed (Trumble et al., 2016). The precise sex-dependent mechanisms that modulate the antibody response are not well understood (56). Further, although sex differences were observed here, this does not explain the interaction with caregiving status and psychological distress evident in this study. Although other caregiving and immune-related studies have also found male caregivers to be more vulnerable (30), this was explained by poorer sleep in these male caregivers relative to female caregivers. However, from a psychological perspective, we found that male caregivers were characterized by higher levels of psychological distress compared to male non-caregivers, and in our three-way interaction model, we found that distress in male caregivers had a negative effect on antibody response compared to the other groups. In addition, it is worth noting that depression is a well-established risk factor for poor immunity (57, 58) including antibody responses (52). As such, this suggests that perhaps it is not necessarily biological sex *per se* driving this but rather gender differences among caregiving experiences that is likely responsible.

While in general female caregivers are found to report higher distress relative to male caregivers (20, 38), here we found that during the COVID-19 pandemic, male caregivers were more psychologically vulnerable and reported high levels of distress. This may relate to findings from studies showing that male and female caregivers differ in how they attend to their emotional reactions but also in their socialisation of using different coping styles (59) with male caregivers being less likely to experience social support (60). Similarly, others have found that male caregivers tend toward a managerial approach, whereas female caregivers generally adopt a relational approach and seek out emotional support from others (61) and these social support factors are associated with reduced distress and better biological health in family caregivers (62, 63) and antibody responses generally (49). Thus, although we did not assess social support, it might be that this lack of support during the pandemic was putting males at greater risk of high distress, a finding captured by recent work on caregivers

from the UK and Ireland (64). It is worth noting an increase in online social support for family caregivers during the pandemic (65), but if male caregivers are less likely to seek emotional support they remain more isolated and distressed. In addition, while studies on gender differences and caregiving during the pandemic are limited, one study found that caregiver burden increased for male caregivers and reduced in female caregivers during the pandemic (26) which may echo some of what we are finding in the present study. In another study, increasing caregiving intensity due to the pandemic was associated with higher caregiver burden for male caregivers but not female caregivers (66), again implying gender-specific effects during the pandemic. Elsewhere, others have found a higher increase in distress symptoms among males as compared to females during the pandemic (67) leading some authors to suggest that there may have been greater resilience and coping among female caregivers during the pandemic (66). As such, the patterns observed here may be pandemic-specific and while they may not be generalisable it does suggest further research is needed. In fact, our findings support the notion that researchers should look at sex-specific aspects of caregiving experiences to help unpack sex/gender differences in health (17). In addition, it also adds to the research on the caregiver-control model of chronic stress which argues that the caregiver context is important for understanding the caregiver-health associations (2, 7, 12).

Although our study has many strengths (e.g., population level study, exclusion of those with prior infection), using questions capturing caregiver status as in other research (68, 69), they did not assess care recipients' illness/disability condition types (e.g., dementia, autism) and studies have found this matters for caregiver health (70, 71) including antibody responses (4, 10). Similarly, other caring-related variables such as length of time caregiving, how chronic or acute the condition is, and the number of people cared for are also important in this context (69, 72-74). Also, we only examined the primary antibody response to a thymus-dependent vaccine, as such we cannot generalize to the thymus-independent vaccines or to secondary immune responses, i.e., antibody levels following a second vaccine shot. However, this would be a fruitful line of enquiry for future research. Further, within the datasets there was no information on the type of COVID-19 vaccine participants had, nor how long since they had received it, i.e., the mean number of days between taking the blood sample and analysis, which might potentially affect antibody responses (75, 76). However, participants did have to return their samples within one week or taking the blood sample. Further, while we cannot know for certain what type of vaccine participants had, the Pfizer-BioNTech

mRNA vaccine was first administered in the UK from December 2020 onwards, it was only given to those over the age of 65, and the Oxford/AstraZeneca viral vector vaccine was the main vaccine administered in the UK to those under this age, at this time, and given the mean age of our participants this is the most likely vaccine for the majority. It is also worth noting that research has found that caregivers are vulnerable to several vaccine types (14). Further, traditionally in stress and vaccine studies, a 1-month follow up is the usual time period to assess peak IgG response (14) but unfortunately we do not have details on how many days post-vaccination blood sampling was or whether this varied by sex. However, given that most of the sample were of similar age, they are likely to have received the vaccine around the same window of time through the coordination of the UK vaccination programme. Finally, although we took account of age, and ethnicity, and checked to see whether distress was driving the between group differences, there are other important factors such as body mass index, sleep, stress, and personality that may be influencing the sex interaction on caregivers' antibody response and might be explored in other datasets.

In summary, our study extends the previous caregiving and antibody response research by showing that male caregivers may be particularly vulnerable immunologically. This finding is also interesting, as by its nature caregiving is heavily gendered, with females more likely to be in caring roles. As such understanding why male caregivers may be more biologically and psychologically vulnerable in this context is worthy of further investigation. Further, our study also confirms that psychosocial factors, i.e. chronic stress of caregiving, are influential for the antibody response to the COVID-19 vaccine (46). Importantly, however, it also suggests that psychosocial interventions for family caregivers, which have positive effects on antibody responses (77), may need to be tailored accordingly for different sexes.

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References

1. Epel ES, Crosswell AD, Mayer SE, Prather AA, Slavich GM, Puterman E, et al. More than a feeling: A unified view of stress measurement for population science. Front Neuroendocrinol. 2018;49:146-69.
2. Whittaker AC, Gallagher S. Caregiving alters immunity and stress hormones: a review of recent research. Current Opinion in Behavioral Sciences. 2019;28:93-7https://doi.org/10.1016/j.cobeha.2019.02.002.
3. Lovell B, Wetherell MA. The cost of caregiving: endocrine and immune implications in elderly and non elderly caregivers. Neurosci Biobehav Rev. 2011;35(6):1342-52.
4. Vedhara K, McDermott MP, Evans TG, Treanor JJ, Plummer S, Tallon D, et al. Chronic stress in nonelderly caregivers: psychological, endocrine and immune implications. J Psychosom Res. 2002;53(6):1153-61.
5. Roth DL, Sheehan OC, Haley WE, Jenny NS, Cushman M, Walston JD. Is Family Caregiving Associated With Inflammation or Compromised Immunity? A Meta-Analysis. Gerontologist. 2019;59(5):e521-e34.
6. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci U S A. 2003;100(15):9090-5.
7. Gallagher S, Bennett KM. Caregiving and allostatic load predict future illness and disability: A population-based study. Brain Behav Immun Health. 2021;16:100295.
8. Prather AA, Epel ES, Portela Parra E, Coccia M, Puterman E, Aiello AE, et al. Associations between chronic caregiving stress and T cell markers implicated in immunosenescence. Brain Behav Immun. 2018;73:546-9.
9. Gouin JP, Hantsoo L, Kiecolt-Glaser JK. Immune dysregulation and chronic stress among older adults: a review. Neuroimmunomodulation. 2008;15(4-6):251-9.
10. Vedhara K, Cox NK, Wilcock GK, Perks P, Hunt M, Anderson S, et al. Chronic stress in elderly carers of dementia patients and antibody response to influenza vaccination. Lancet. 1999;353(9153):627-31.
11. Glaser R, Sheridan J, Malarkey WB, MacCallum RC, Kiecolt-Glaser JK. Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. Psychosom Med. 2000;62(6):804-7.
12. Gallagher S, Phillips AC, Drayson MT, Carroll D. Parental caregivers of children with developmental disabilities mount a poor antibody response to pneumococcal vaccination. Brain Behav Immun. 2009;23(3):338-46.
13. Gallagher S, Phillips AC, Drayson MT, Carroll D. Caregiving for children with developmental disabilities is associated with a poor antibody response to influenza vaccination. Psychosom Med. 2009;71(3):341-4.
14. Burns VE, Gallagher S. Antibody response to vaccination as a marker of in vivo immune function in psychophysiological research. Neurosci Biobehav Rev. 2010;35(1):122-6.
15. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: A quantitative review. Vaccine. 2006;24(8):1159-69.
16. Boraschi D, Italiani P. Immunosenescence and vaccine failure in the elderly: Strategies for improving response. Immunology Letters. 2014;162(1, Part B):346-53.
17. Xiong C, Biscardi M, Astell A, Nalder E, Cameron JI, Mihailidis A, et al. Sex and gender differences in caregiving burden experienced by family caregivers of persons with dementia: A systematic review. PLoS One. 2020;15(4):e0231848.
18. Klein SL, Flanagan KL. Sex differences in immune responses. Nature Reviews Immunology. 2016;16(10):626-38.
19. Fischinger S, Boudreau CM, Butler AL, Streeck H, Alter G. Sex differences in vaccine-induced humoral immunity. Semin Immunopathol. 2019;41(2):239-49.

20. Morgan T, Ann Williams L, Trussardi G, Gott M. Gender and family caregiving at the end-of-life in the context of old age: A systematic review. Palliat Med. 2016;30(7):616-24.
21. Lee Y, Tang F. More caregiving, less working: caregiving roles and gender difference. J Appl Gerontol. 2015;34(4):465-83.
22. Williams LA, Giddings LS, Bellamy G, Gott M. 'Because it's the wife who has to look after the man': A descriptive qualitative study of older women and the intersection of gender and the provision of family caregiving at the end of life. Palliat Med. 2017;31(3):223-30.
23. CarersUK. Facts & figures. https://wwwcarersukorg/news-and-campaigns/press-releases/facts-and-figures. 2021.
24. Pinquart M, Sörensen S. Gender Differences in Caregiver Stressors, Social Resources, and Health: An Updated Meta-Analysis. The Journals of Gerontology: Series B. 2006;61(1):P33-P45.
25. van Knippenberg RJM, de Vugt ME, Ponds RW, Verhey FRJ, Myin-Germeys I. Emotional reactivity to daily life stress in spousal caregivers of people with dementia: An experience sampling study. PLoS One. 2018;13(4):e0194118.
26. Raiber K, Verbakel E. Are the gender gaps in informal caregiving intensity and burden closing due to the COVID-19 pandemic? Evidence from the Netherlands. Gend Work Organ. 2021;28(5):1926-36.
27. Russell BS, Hutchison M, Tambling R, Tomkunas AJ, Horton AL. Initial Challenges of Caregiving During COVID-19: Caregiver Burden, Mental Health, and the Parent-Child Relationship. Child Psychiatry Hum Dev. 2020;51(5):671-82.
28. Thompson RL, Lewis SL, Murphy MR, Hale JM, Blackwell PH, Acton GJ, et al. Are there Sex Differences in Emotional and Biological Responses in Spousal Caregivers of Patients with Alzheimer's Disease? Biological Research For Nursing. 2004;5(4):319-30.
29. Mortensen J, Dich N, Clark AJ, Ramlau-Hansen CH, Head J, Kivimäki M, et al. Informal caregiving and diurnal patterns of salivary cortisol: Results from the Whitehall II cohort study. Psychoneuroendocrinology. 2019;100:41-7.
30. Mills PJ, Ancoli-Israel S, Känel Rv, Mausbach BT, Aschbacher K, Patterson TL, et al. Effects of gender and dementia severity on Alzheimer's disease caregivers' sleep and biomarkers of coagulation and inflammation. Brain, Behavior, and Immunity. 2009;23(5):605-10.
31. Adler KA, Patterson TL, Grant I. Physiological challenges associated with caregiving among men. In B. J. Kramer & E. H. Thompson (Eds.), Men as caregivers: Theory, research, and service implications (pp. 127–150). Springer Publishing Company. 2002.
32. Li J, Cowden LG, King JD, Briles DA, Schroeder HW, Jr., Stevens AB, et al. Effects of Chronic Stress and Interleukin-10 Gene Polymorphisms on Antibody Response to Tetanus Vaccine in Family Caregivers of Patients With Alzheimer's Disease. Psychosomatic Medicine. 2007;69(6).
33. Wong SY, Wong CK, Chan FW, Chan PK, Ngai K, Mercer S, et al. Chronic psychosocial stress: does it modulate immunity to the influenza vaccine in Hong Kong Chinese elderly caregivers? Age (Dordr). 2013;35(4):1479-93.
34. Gallagher S, Howard S, Muldoon OT, Whittaker AC. Social cohesion and loneliness are associated with the antibody response to COVID-19 vaccination. Brain Behav Immun. 2022;103:179-85.
35. Jensen A, Stromme M, Moyassari S, Chadha AS, Tartaglia MC, Szoeke C, et al. COVID-19 vaccines: Considering sex differences in efficacy and safety. Contemp Clin Trials. 2022;115:106700.
36. Danielsen AC, Lee KMN, Boulicault M, Rushovich T, Gompers A, Tarrant A, et al. Sex disparities in COVID-19 outcomes in the United States: Quantifying and contextualizing variation. Social Science & Medicine. 2022;294:114716.
37. Dellafiore F, Arrigoni C, Nania T, Caruso R, Baroni I, Vangone I, et al. The impact of COVID-19 pandemic on family caregivers' mental health: a rapid systematic review of the current evidence. Acta Biomed. 2022;93(S2):e2022154.
38. Gallagher S, Wetherell MA. Risk of depression in family caregivers: unintended consequence of COVID-19. BJPsych Open. 2020;6(6):e119.

39. Moynihan JA, Larson MR, Treanor J, Duberstein PR, Power A, Shore B, et al. Psychosocial Factors and the Response to Influenza Vaccination in Older Adults. Psychosomatic Medicine. 2004;66(6).
40. Kaneko H, Tsuboi H. Depressive symptoms predict antibody titers after a second dose of the SARS-CoV-2 BNT162b2 vaccine among hospital workers in Japan. Brain, Behavior, and Immunity. 2023;107:414-8.
41. Understanding Society. University of Essex, Institute for Social and Economic Research. (2021). Understanding Society: COVID-19 Study, 2020-2021. [data collection]. . 10th Edition UK Data Service SN: 8644, DOI: 105255/UKDA-SN-8644-1. 2020-21.
42. Phillips AC. The vaccination model in psychoneuroimmunology research: a review. Methods Mol Biol. 2012;934:355-70.
43. Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O, et al. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. Psychological Medicine. 1997;27(1):191-7.
44. Gallagher S, Wetherell MA. Risk of depression in family caregivers: unintended consequence of COVID-19. BJPsych Open. 2020;6(6):e119-e.
45. Pang NY-L, Pang AS-R, Chow VT, Wang D-Y. Understanding neutralising antibodies against SARS-CoV-2 and their implications in clinical practice. Military Medical Research. 2021;8(1):47.
46. Madison AA, Shrout MR, Renna ME, Kiecolt-Glaser JK. Psychological and Behavioral Predictors of Vaccine Efficacy: Considerations for COVID-19. Perspectives on Psychological Science. 2021;16(2):191-203.
47. Kaminska O, Lynn. P. Weighting and Sample Representation: Frequently Asked Questions. Understanding Society: UK Household Longitudinal Study. 2019;https://www.understandingsociety.ac.uk/sites/default/files/downloads/documentation/user-guides/mainstage/weighting_faqs.pdf.
48. Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis, Second Edition: A Regression-Based Approach. Guildford Press, London. 2017;ISBN 9781462534654.
49. Gallagher S, Phillips AC, Ferraro AJ, Drayson MT, Carroll D. Psychosocial factors are associated with the antibody response to both thymus-dependent and thymus-independent vaccines. Brain Behav Immun. 2008;22(4):456-60.
50. Phillips AC, Burns VE, Carroll D, Ring C, Drayson M. The association between life events, social support, and antibody status following thymus-dependent and thymus-independent vaccinations in healthy young adults. Brain, Behavior, and Immunity. 2005;19(4):325-33.
51. Cohen S, Miller GE, Rabin BS. Psychological stress and antibody response to immunization: a critical review of the human literature. Psychosom Med. 2001;63(1):7-18.
52. Madison AA, Shrout MR, Renna ME, Kiecolt-Glaser JK. Psychological and Behavioral Predictors of Vaccine Efficacy: Considerations for COVID-19. Perspect Psychol Sci. 2021;16(2):191-203.
53. Takita M, Yoshida T, Tsuchida T, Nakagama Y, Kido Y, Suzuki S, et al. Low SARS-CoV-2 antibody titers may be associated with poor clinical outcomes for patients with severe COVID-19. Scientific Reports. 2022;12(1):9147.
54. Vedhara K. Vaccines: The Good the Bad and the Ugly. The Psychologist British Psychological Society 2020;https://thepsychologist.s3.eu-west-2.amazonaws.com/articles/pdfs/0720vedhara.pdf?X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Credential=AKIA3JJOMCSRX35UA6UU%2F20211220%2Feu-west-2%2Fs3%2Faws4_request&X-Amz-Date=20211220T131249Z&X-Amz-SignedHeaders=Host&X-Amz-Expires=10&X-Amz-Signature=c13157189dba13c1e8460b83e58d8ba09359b3d5df360a409644e12347324153(33):36-9.
55. Ruggieri A, Anticoli S, D'Ambrosio A, Giordani L, Viora M. The influence of sex and gender on immunity, infection and vaccination. Ann Ist Super Sanita. 2016;52(2):198-204.
56. Griesbeck M, Scully E, Altfeld M. Sex and gender differences in HIV-1 infection. Clin Sci (Lond). 2016;130(16):1435-51.

57. Vasile C. Mental health and immunity (Review). Exp Ther Med. 2020;20(6):211.
58. Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, et al. The Relationship of Depression and Stressors to Immunological Assays: A Meta-Analytic Review. Brain, Behavior, and Immunity. 2001;15(3):199-226.
59. Lutzky SM, Knight BG. Explaining gender differences in caregiver distress: the roles of emotional attentiveness and coping styles. Psychol Aging. 1994;9(4):513-9.
60. Greenwood N, Smith R. Barriers and facilitators for male carers in accessing formal and informal support: A systematic review. Maturitas. 2015;82(2):162-9.
61. Hong S-c, Coogle CL. Spousal Caregiving for Partners With Dementia: A Deductive Literature Review Testing Calasanti's Gendered View of Care Work. Journal of Applied Gerontology. 2014;35(7):759-87.
62. Gallagher S, Whiteley J. Social support is associated with blood pressure responses in parents caring for children with developmental disabilities. Res Dev Disabil. 2012;33(6):2099-105.
63. Cantwell J, Muldoon OT, Gallagher S. Social support and mastery influence the association between stress and poor physical health in parents caring for children with developmental disabilities. Res Dev Disabil. 2014;35(9):2215-23.
64. Linden M, Leonard R, Forbes T, Brown M, Marsh L, Todd S, et al. Experiences of UK and Irish family carers of people with profound and multiple intellectual disabilities during the COVID-19 pandemic. BMC Public Health. 2023;23(1):2475.
65. Daynes-Kearney R, Gallagher S. Online Support Groups for Family Caregivers: Scoping Review. J Med Internet Res. 2023;25:e46858.
66. Cohen SA, Kunicki ZJ, Drohan MM, Greaney ML. Exploring Changes in Caregiver Burden and Caregiving Intensity due to COVID-19. Gerontol Geriatr Med. 2021;7:2333721421999279.
67. Wister A, Li L, Mitchell B, Wolfson C, McMillan J, Griffith LE, et al. Levels of Depression and Anxiety Among Informal Caregivers During the COVID-19 Pandemic: A Study Based on the Canadian Longitudinal Study on Aging. The Journals of Gerontology: Series B. 2022;77(9):1740-57.
68. Gallagher S, Phillips AC, Evans P, Der G, Hunt K, Carroll D. Caregiving is associated with low secretion rates of immunoglobulin A in saliva. Brain, Behavior, and Immunity. 2008;22(4):565-72.
69. Schulz R, Beach SR. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. JAMA. 1999;282(23):2215-9.
70. Pinquart M, Sorensen S. Differences between caregivers and noncaregivers in psychological health and physical health: a meta-analysis. Psychol Aging. 2003;18(2):250-67.
71. Gallagher S, Pilch M, Hannigan A. Prior depressive symptoms and persistent child problem behaviours predict future depression in parents of children with developmental disabilities: The growing up in Ireland cohort study. Res Dev Disabil. 2018;80:170-9.
72. Scott LD, Hwang WT, Rogers AE. The impact of multiple care giving roles on fatigue, stress, and work performance among hospital staff nurses. J Nurs Adm. 2006;36(2):86-95.
73. Litzelman K, Skinner HG, Gangnon RE, Nieto FJ, Malecki K, Witt WP. The relationship among caregiving characteristics, caregiver strain, and health-related quality of life: evidence from the Survey of the Health of Wisconsin. Qual Life Res. 2015;24(6):1397-406.
74. Gallagher S, Hannigan A. Depression and chronic health conditions in parents of children with and without developmental disabilities: The growing up in Ireland cohort study. Research in Developmental Disabilities. 2014;35(2):448-54.
75. Burns VE, Gallagher S. Antibody response to vaccination as a marker of in vivo immune function in psychophysiological research. Neuroscience & Biobehavioral Reviews. 2010;35(1):122-6.
76. Jacobsen H, Sitaras I, Katzmarzyk M, Cobos Jiménez V, Naughton R, Higdon MM, et al. Systematic review and meta-analysis of the factors affecting waning of post-vaccination neutralizing antibody responses against SARS-CoV-2. npj Vaccines. 2023;8(1):159.
77. Vedhara K, Bennett PD, Clark S, Lightman SL, Shaw S, Perks P, et al. Enhancement of Antibody Responses to Influenza Vaccination in the Elderly following a Cognitive-Behavioural Stress Management Intervention. Psychotherapy and Psychosomatics. 2003;72(5):245-52.

Table 1. Socio-demographics, health, and outcome variables across caregiver groups

Variable	**Non-carers (*N*=378)**	**Carers (*N*=168)**	**Test of difference**
Age	59.17(19.06)	60.82(16.46)	F (1,542) = 0.922, p =.33
Living with partner (yes) %	84.7	87.5	χ^2 (1) = 0.672, p < .41
Sex (female) %	51.3	61.5	χ^2 (1) = 21.00, p < .001
Ethnicity % (White)	97.4	97.3	χ^2 (1) = 0.006, p = .93
Income (Annual £)	14,216 (54,954)	14,775 (26,812)	F (1,386) = .015, p = .90
Health Condition % (yes)	63.0	65.1	χ^2 (1) = 0.21, p =.64
Smoker %(yes)	4.6	9.2	χ^2 (1) = 4.09, p =.043
Alcohol intake last month % (yes)	73.2	69.7	χ^2 (1) =0.68, p =.40
Fruit (portions) per day	2.37 (1.23)	2.54(1.30)	F (1,542) = 2.21, p = .14
Vegetable (portions) per day	2.89 (1.18)	2.89(1.41)	F (1,535) = .003, p = .95
Days Walking (0-7 days)	4.95(2.14)	5.10(2.11)	F (1,504) = .512, p = .47
GHQ-12	10.99 (4.79)	12.04(5.44)	F (1,542) = 7.53, p = .006

Tests of differences include ANOVA (F-tests) and Chi-squared (χ^2)

Table 2. Socio-demographics, health and outcome variables across males and females

Variable	**Males (N=230)**	**Females (N=316)**	**Test of difference**
Age	64.75 (19.42)	55.64(18.41)	F (1,542) = 24.60, p < .001
Living with partner (yes) %	73.4	60.9	χ^2 (1) = 11.27, p < *.001*
Ethnicity % (White)	91.9	96.9	χ^2 (1) = 6.95, p = .008
Income (Annual £)	23,795 (77,786)	17,485 (31,604)	F (1,386) = 1.32, p = .25
Health Condition % (yes)	69.2	61.5	χ^2 (1) =.059, p =.80
Smoker %(yes)	0.7	9.99	χ^2 (1) = 23.01, p < .001
Alcohol intake last month %(yes)	72.3	71.7	χ^2 (1) =0.82 p = .36
Fruit (portions) per day	3.17 (0.71)	3.09(0.95)	F (1,538) = 0.54, p = .46
Vegetable (portions) per day	2.95 (1.56)	2.90(1.15)	F (1,530) = .19, p = .65
Days Walking (0-7 days)	5.04(2.20)	4.96(2.06)	F (1,494) = 0.70, p = .78
GHQ-12	10.93 (5.00)	11.91(4.92)	F (1,539 = 5.89, p = .016

Tests of differences include ANOVA (F-tests) and Chi-squared (χ^2)

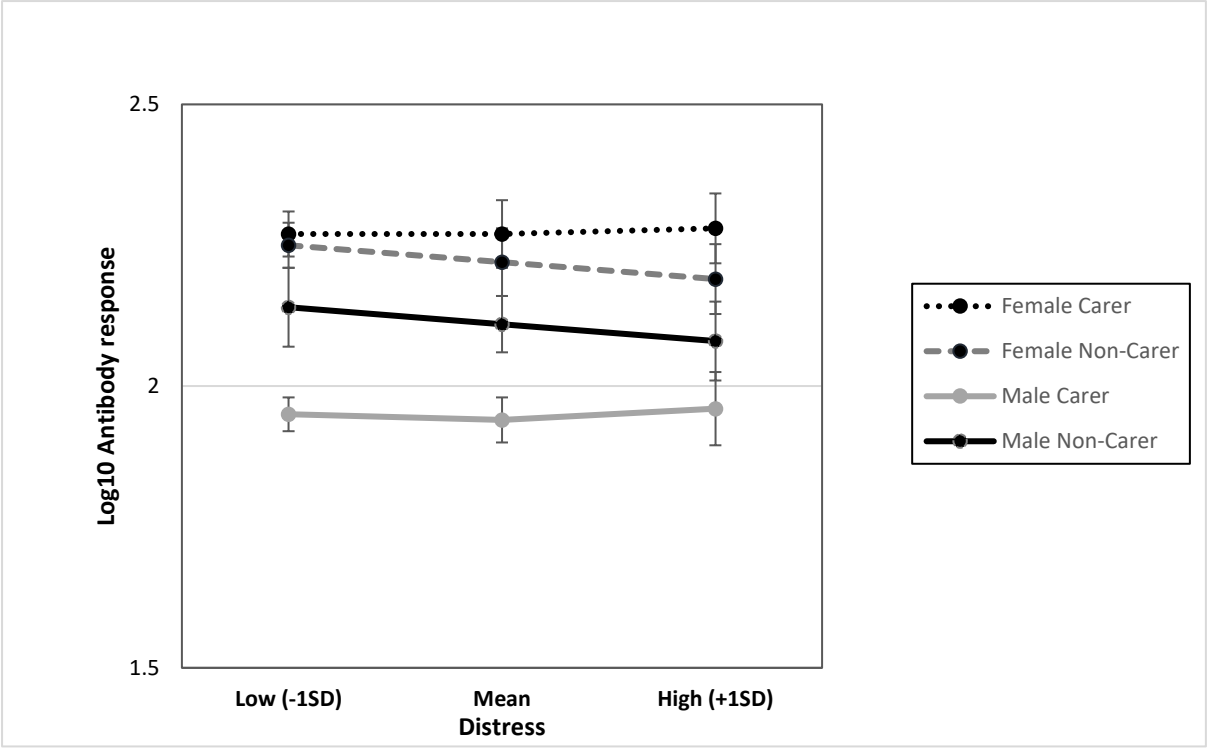

Figure 1 Caption: Interaction between caregiver status X sex X distress on antibody response showing that male caregivers had the lowest responses at both low and mean levels of depression compared to other groups. Error bars are standard errors.