List of Abbreviations

APC	Admitted Patient Care
CES-D	Centre for Epidemiological Studies Depression
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CSH	Cause-Specific Hazard
ELSA	English Longitudinal Study of Ageing
HES	Hospital Episode Statistics
HR	Hazard Ratio
HSE	Health Survey in England
ICD-10	International Statistical Classification of Disease and Related Health Problems 10th Revision
RD	Respiratory Disease
RMSEA	Root Mean Square Error of Approximation
TLI	Tucker–Lewis Index
WLSMV	Mean- and Variance-adjusted Weighted Least Squares

Methods

Participants

The English Longitudinal Study of Ageing (ELSA) is a large-scale panel study of people aged 50 and over and their partners, living in private households in England. The original sample was drawn from participants from the Health Survey in England (HSE) in 1998, 1999 and 2001 [1]. The first wave of data collection commenced in 2002/2003, and participants have been followed biennially since. We used wave 4 (2008/9) as our baseline because some of our variables of interest were not measured at earlier waves. We restricted participants to core

ELSA members who had returned the self-completion questionnaire where most of our main variables of interest were measured (N=8310). The information on RD admissions was obtained through data linkage with the Admitted Patient Care (APC) data from NHS Hospital Episode Statistics (HES). Further, in order to consider the competing risk of death over the follow-up period, ELSA was linked with mortality data obtained from the UK National Health Service mortality registry. ELSA participants who did not consent to data linkage were dropped from the analysis (13%), leaving a sample of 7270 participants. Our analyses also used spirometric data collected through nurse visits, so the 10% of participants with missing spirometric data were excluded, leaving a sample of 6563 participants. After dropping cases with missing data on exposures or covariates (32%), our final analytical sample was 4478 participants (see Figure S1).

Measures

Respiratory disease (RD) diagnoses were derived from the APC data, based on the International Statistical Classification of Disease and Related Health Problems 10th Revision (ICD-10) codes, as from J00 to J99. RD admissions could be divided into four groups: acute RD (ICD-10: J00-J06, J30-J39, J09-J22 J680-J682 J80-J82, J85, J86), chronic RD (J40-J47, J60-J67 J683-J689 J69 J70, J84), pleural RD (J90-J94) and other RD (J95-J99). The APC data were available until January 2018, providing a maximum follow-up of 9.6 years.

Given people with pre-existing RDs are likely to be at an increased risk of having an admission, it is important to account specifically for pre-existing respiratory conditions. These were derived from baseline questions relating to self-reported chronic lung diseases, such as asthma, chronic bronchitis, and emphysema. However, people could be unaware of their lung conditions. For example, it was reported that approximately one third of individuals admitted

to hospital with a first exacerbation of Chronic Obstructive Pulmonary Disease (COPD), had not previously been diagnosed [2]. Therefore, we combined self-reported conditions with spirometric assessments from the baseline to identify individuals with potentially undiagnosed COPD, defined as having an FEV1/FVC ratio less than 0.7 [3]. Overall, this led to an index comprised of the following categories: known COPD diagnosis, potentially undiagnosed COPD, and no COPD.

Social isolation

Social isolation was measured in three different ways. Living alone was coded as a binary variable to capture domestic isolation. The second was low social contact. Participants were asked how much they did the following activities with their children, relatives and friends respectively, including: 1) meet up 2) speak on the phone. Responses ranged from 1) three or more times a week to 6) less than once a year or never. An index was derived from confirmatory factor analysis (CFA) using the mean- and variance-adjusted weighted least squares (WLSMV) estimator (RMSEA=0.05, CFI=1.00, TLI=1.00), with higher values indicating lower social contact.

Finally, social disengagement was measured by the frequency of: 1) group membership (e.g. political party, resident groups, religious groups, social clubs etc.), 2) formal volunteering and 3) engagement with community cultural activities (including going to museums, exhibitions, the theatre, concerts, opera or the cinema). Group membership was coded into three categories: 3) none, 2) one, and 1) at least two. Responses to formal volunteering were as 5) never, 4) one-off activity, 3) less often, 2) less than once a week but at least once a month, and 1) at least once a week. Frequency of cultural activities ranged from 6) never, to 1) twice a month or more. A total score was generated from CFA using the WLSMV estimator, with

higher scores indicating higher levels of social disengagement (RMSEA=0.00, CFI=1.00, TLI=1.00).

Loneliness

Loneliness is a cognitive evaluation of the quantity and quality of one's existing social relationships [4]. It is sometimes referred as perceived or subjective social isolation [5]. Loneliness was measured using the three-item subscale from the revised UCLA loneliness scale[6]. The questions include: 1) how often do you feel lack companionship? 2) how often do you feel isolated from others? 3) how often do you feel left out? Responses to each question were scored on a three-point Likert scale ranging from hardly ever/never, to some of the time, to often. A loneliness index was derived from CFA model using the WLSMV estimator designed for ordinal data (RMSEA=0.00, CFI=1.00, TLI=1.00). A higher value meant a higher level of loneliness.

Covariates

Our analyses included potential confounders in the relationship between social factors and RD admissions. These included socio-demographic confounders, such as gender, age groups (50-59, 60-69, 70-79, 80+), ethnicity (white vs. non-white), and socio-economic status (an index generated using principle component analysis based on education, social class and household wealth) [7]. Additionally, we included an index of living environment deprivation (a domain of the English index of multiple deprivation) that could affect respiratory health. This took into account both indoor (e.g. central heating) and outdoor living environment (e.g. air quality) [8]. Further, our analyses included health-related confounders, including pre-existing RD conditions as explained above, a binary variable of comorbidity, and a depression index. Depression was measured using the eight-item Centre for Epidemiological Studies Depression (CES-D) scale. The depression index was generated from CFA using WLSMV estimator

(RMSEA=0.03, CFI=1.00, TLI=1.00). Finally, we also considered behavioural confounders, including smoking (never smoked, ex-smoker, current smoker), heavy drinking (almost every day and above 14 units last week), healthy diet (5 or more portions of vegetables or fruits per day) and physically active (vigorous or moderate physical activity at least once a week).

Statistical Analysis

Survival analysis was used to model the time from the baseline interview until a RD admission or until the end of the follow-up period if participants had no admission. Mortality was treated as a competing risk event as it precluded the occurrence of RD admissions. We adopted the Cox cause-specific hazards (CSH) modelling approach by censoring participants at the time of death [9 10]. CSH models were built in a sequence of steps, introducing explanatory variables following the order of: 1) social isolation and loneliness, 2) socio-demographics, 3) health, and 4) behavioural factors.

Sensitivity analyses based on multiple imputation were performed to assess the influence of missing data. Thirty-five complete datasets were generated by chained equations using the *mi impute chained* command in Stata. Estimates from these datasets were combined based on Rubin's rule [11]. A variety of further sensitivity analyses were carried out, for example, to exclude participants who had RD admissions before the baseline and to test the influence of mortality from RD. We tested moderation effects by introducing interaction terms and stratifying the sample. CFA scores with WLSMV estimators were generated in R 3.5.1, but the main analyses were carried out using Stata v15.

Results

A total of 11% of participants had a RD admission within the follow-up period (Figure S2). A further 9% of participants died without a RD admission, and 80% had no event. Among

participants with a RD admission, 64% of them had a primary diagnosis of acute RD, 26% had a primary diagnosis of chronic RD, 5% of pleural diseases and 5% of other RD. Due to the small number of cases in the sub-categories, we did not distinguish different types of RD in the main analysis.

Of our sample, 54% were female and 22% lived alone. The sample was predominantly of white ethnicity. 13% of participants had a diagnosed pre-existing lung condition, and an additional 21% had potentially undiagnosed obstructive lung disease such as COPD. Over 60% had at least one comorbidity. Demographics for the full sample and sub-groups are provided in Table S1.

Discussion

This study found that living alone and social disengagement are risk factors for RD hospital admissions. However, there was no evidence that low social contact or loneliness are related to RD admissions. These findings were robust to multiple sensitivity analyses. Our results are broadly supportive of other research that suggests that social factors, including aspects of social isolation, are associated with an increased risk of hospital admission [12 13].

A number of possible underlying mechanisms have been suggested to explain the influence of social isolation and loneliness on health. A well-accepted explanation is that they affect life style and health behaviours through social support or peer pressure [14 15]. For instance, it has been reported that lonely and socially isolated people are at a greater risk of being physically inactive and smoking [16], both of which increase the risk of RD. Therefore, social relationships could help to prevent health condition progression and subsequent major incidents like hospital admission and death through moderating maladaptive behaviours. However, our analyses showed persistent association even after accounting for these factors, suggesting

that they do not entirely explain the relationship. Another possibility is that individuals who live alone or are socially disengaged may have less social pressure to seek medical attention early in the development of a respiratory disease. Receiving prompt antibiotics in the community for a non-severe lower respiratory tract infection may prevent progression of the illness and therefore avoid a hospital admission or death. Further, biological factors could help to explain the relationship. Indeed, social isolation has recently been shown to be associated with increased inflammation [17]. Systemic and pulmonary inflammation is an important aetiological factor in a variety of respiratory diseases including COPD [18], asthma [19], and bronchiectasis [20]. Furthermore, chronic system inflammation may also play a key role in the aetiology of comorbidities associated with chronic lung diseases such as COPD [21].

Further, it is important to note that our discussion is around RD hospital admissions, which are influenced not only by disease progression or severity but also human decisions. The relationship between hospital admission and living alone may be driven, at least in part, by the patient's social situation impacting a physician's decision on whether to admit a patient, as living alone is associated with poor health, disability and risk of falls [22]. For borderline decisions regarding hospital admission, the perceived safety of the place of residence is a key consideration, so this could provide further explanation for the finding relating to living alone.

Our results call attention to the distinctions across different social isolation measures. Loneliness is a cognitive evaluation of the quantity and quality of one's existing social relationships [23]. It is sometimes referred as perceived or subjective social isolation [5], in contrast to objective measures such as living alone, low social contact and social disengagement. In this study, we have found no evidence that loneliness affects RD events, but persistent associations for the objective measures, more specifically living alone and social

disengagement. From this, it is tempting to jump to the conclusion that objective isolation matters, but not subjective appraisals. However, we should note that one of the objective measures, low social contact, was also not associated with RD events. It is possible that social contact carries with it increased risk of contagious respiratory conditions; more so than living with somebody (where there is a restricted germ pool) or social engagement (which might not involve close person-to-person contact in the same way as seeing family or friends socially). As such, the potential benefits of social contact may be attenuated via the increased risk of infection. However, this remains to be explored further.

One of the main strengths of our study is the use of data from large-scale nationally representative survey linked with administrative mortality and hospital records. As such, our findings have good external validity and could be generalised to older people in England. Our study also uses a longitudinal research design with a follow-up period up to nearly 10 years, subject to little influence of attrition thanks to the data linkage to administrative records. Moreover, in our analyses, we have considered a comprehensive range of all identified confounding factors. A number of limitations, however, are important to consider. As an observational study, causality cannot be assumed, as measurement error or residual unidentified confounding may affect results. In addition, limited by data availability, this paper focused on hospital admission and death. Future work will benefit from looking at also prescriptions, the utilisation of primary care services, as well as Accident and Emergency services. This will contribute to a full picture of how loneliness and isolation is related to health service utilisation due to respiratory diseases.

In conclusion, our study provides strong evidence that living alone and social disengagement are risk factors for hospital admissions for respiratory disease. This has two main clinical

implications. First, older adults living alone, and in particular those at risk due to existing chronic lung diseases, may benefit from additional targeted health service input in the community setting to try and prevent developing respiratory problems from requiring hospital admission. Further, given the roll out of social prescribing across England currently, whereby individuals with or at risk of chronic conditions can be referred to community programmes such as those included in our social engagement variable, future studies could explore whether referring those at risk of RD to such activities helps to reduce the incidence of RD hospital admissions.

Supplementary Figures

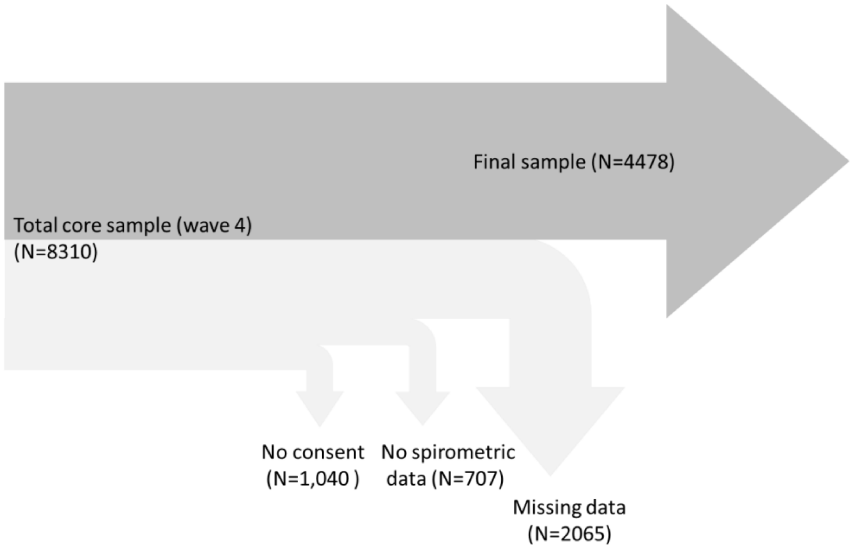

Figure S1. Sample selection diagram

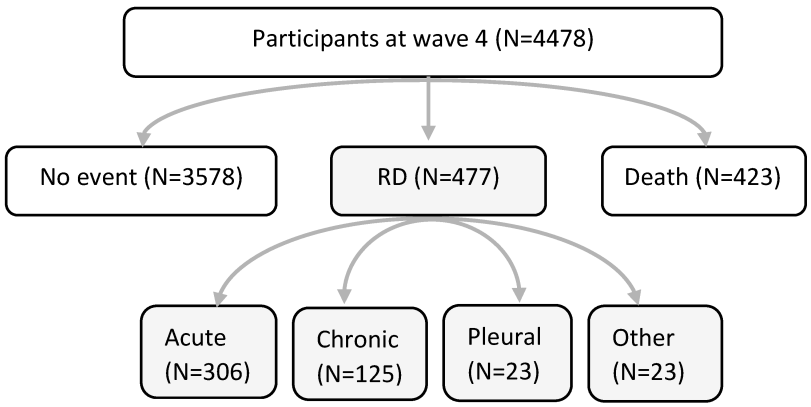

Figure S2. Frequency of respiratory disease (RD) events

Supplementary Tables

Table S1. Summary statistics of participants at wave 4

	All (N=4478)	No event (N=3578)	RD admission (N=477)	Death (N=423)
Social isolation and loneliness				
Living alone	22.40	19.09	33.96	37.35
Low social contact	-2.52-2.57†	-0.01 (0.99)	0.00 (1.06)	0.05 (1.04)
Social disengagement	-3.13-1.79†	-0.08 (0.98)	0.41 (0.97)	0.24 (1.02)
Loneliness	-1.42-3.27†	-0.04 (0.97)	0.19 (1.10)	0.14 (1.11)
Socio-demographic				
Female	53.68	55.03	48.22	48.46
Age				
50-59	27.98	31.92	16.35	7.80
60-69	41.40	44.24	32.29	27.66
70-79	23.29	20.71	32.49	34.75
80+	7.32	3.13	18.87	29.79
Non-white, %	1.47	1.51	1.26	1.42
Socioeconomic status (SES) index	-2.12-1.60†	0.07 (0.99)	-0.33 (1.00)	-0.22 (1.02)
Living environment deprivation	-1.24-4.51†	-0.02 (0.99)	0.05 (1.06)	0.08 (0.98)
Health				
Pre-existing condition				
No COPD	65.81	70.04	43.61	55.08
Potentially undiagnosed COPD	21.28	19.45	26.00	31.44
Diagnosed COPD	12.91	10.51	30.40	13.48
Comorbidity				
None	39.59	42.51	28.72	27.19
One	40.38	40.02	41.30	42.32
Two or more	20.03	17.47	29.98	30.50
Depression score	-0.80-3.21†	-0.06 (0.97)	0.35 (1.10)	0.15 (1.04)
Behavioural				
Smoking				
Never smoked	40.67	43.10	28.30	34.04
Ex-smoker	47.57	46.79	50.10	51.30
Current smoker	11.77	10.12	21.59	14.66
Heavy drinking	13.47	13.11	13.42	16.55
Healthy diet	56.86	58.11	48.64	55.56
Physically active	82.87	86.50	66.88	70.21

Notes: † The numeric indices were standardised with mean to 0 and standard deviation to 1

Table S2. Estimates from multiple imputation Cox models (N=6563, Imputation=35)

	Model I	Model II	Model III	Model IV
Living alone	1.80	1.32	1.28	1.23
	P=0.000	P=0.001	P=0.003	P=0.015
	[1.55—2.10]	[1.12—1.55]	[1.09—1.51]	[1.04—1.45]
Low social contact	1.01	0.98	1.00	0.99
	P=0.717	P=0.653	P=0.895	P=0.885
	[0.94—1.09]	[0.92—1.06]	[0.93—1.07]	[0.93—1.07]
Social disengagement	1.57	1.43	1.34	1.24
	P=0.000	P=0.000	P=0.000	P=0.000
	[1.46—1.70]	[1.31—1.56]	[1.22—1.46]	[1.13—1.35]
Loneliness	1.04	1.09	0.95	0.95
	P=0.236	P=0.014	P=0.193	P=0.228
	[0.97—1.11]	[1.02—1.17]	[0.88—1.03]	[0.86—1.03]

Notes: Model I was unadjusted; Model II controlled for socio-demographic confounders; Model III additionally controlled for health-related confounders; Model IV additionally controlled for behavioural confounders

Table S3. Estimates from Cox models grouping RD death with RD admissions (N=4478)

	Model I	Model II	Model III	Model IV
Living alone	1.90	1.43	1.38	1.33
	P=0.000	P=0.001	P=0.003	P=0.008
	[1.56—2.31]	[1.16—1.77]	[1.12—1.71]	[1.08—1.65]
Low social contact	0.98	0.95	0.96	0.96
	P=0.672	P=0.290	P=0.343	P=0.342
	[0.90—1.07]	[0.88—1.04]	[0.88—1.05]	[0.88—1.05]
Social disengagement	1.55	1.39	1.31	1.22
	P=0.000	P=0.000	P=0.000	P=0.000
	[1.41—1.70]	[1.25—1.54]	[1.18—1.45]	[1.09—1.36]
Loneliness	1.05	1.08	0.95	0.95
	P=0.276	P=0.099	P=0.326	P=0.282
	[0.96—1.14]	[0.99—1.17]	[0.87—1.05]	[0.86—1.04]

Notes: Model I was unadjusted; Model II controlled for socio-demographic confounders; Model III additionally controlled for health-related confounders; Model IV additionally controlled for behavioural confounders

Table S4. Estimates from Cox models excluding people with previous admissions in the last five years (N=4346)

	Model I	Model II	Model III	Model IV
Living alone	1.82	1.39	1.34	1.29
	P=0.000	P=0.005	P=0.011	P=0.029
	[1.47—2.26]	[1.11—1.75]	[1.07—1.69]	[1.03—1.63]
Low social contact	1.01	0.97	0.98	0.98
	P=0.887	P=0.555	P=0.687	P=0.695
	[0.92—1.10]	[0.89—1.07]	[0.89—1.08]	[0.89—1.08]
Social disengagement	1.53	1.39	1.32	1.23
	P=0.000	P=0.000	P=0.000	P=0.001
	[1.39—1.69]	[1.24—1.56]	[1.18—1.48]	[1.09—1.38]
Loneliness	1.03	1.06	0.94	0.94
	P=0.589	P=0.239	P=0.260	P=0.224
	[0.93—1.13]	[0.96—1.16]	[0.85—1.05]	[0.84—1.04]

Notes: Model I was unadjusted; Model II controlled for socio-demographic confounders; Model III additionally controlled for health-related confounders; Model IV additionally controlled for behavioural confounders

Table S5. Estimates from Cox models on acute RD (N=4478)

	Model I	Model II	Model III	Model IV
Living alone	1.87	1.38	1.34	1.34
	P=0.000	P=0.021	P=0.033	P=0.033
	[1.46—2.41]	[1.05—1.81]	[1.02—1.76]	[1.02—1.77]
Low social contact	0.99	0.96	0.97	0.97
	P=0.872	P=0.447	P=0.555	P=0.617
	[0.89—1.11]	[0.86—1.07]	[0.87—1.08]	[0.87—1.08]
Social disengagement	1.48	1.33	1.27	1.23
	P=0.000	P=0.000	P=0.000	P=0.003
	[1.32—1.66]	[1.17—1.52]	[1.11—1.45]	[1.07—1.41]
Loneliness	1.01	1.04	0.92	0.92
	P=0.830	P=0.504	P=0.190	P=0.211
	[0.91—1.13]	[0.93—1.16]	[0.81—1.04]	[0.81—1.05]

Notes: Model I was unadjusted; Model II controlled for socio-demographic confounders; Model III additionally controlled for health-related confounders; Model IV additionally controlled for behavioural confounders

Table S6. Estimates from Cox models with gender interaction terms (N=4478)

	Model IV + interaction (women* living alone)	Model IV + interaction (women*disengagement)
Living alone	1.28 P=0.124 [0.94—1.74]	1.32 P=0.012 [1.06—1.64]
Low social contact	0.96 P=0.325 [0.88—1.04]	0.96 P=0.327 [0.88—1.04]
Social disengagement	1.24 P=0.000 [1.11—1.38]	1.24 P=0.003 [1.08—1.44]
Loneliness	0.95 P=0.327 [0.86—1.05]	0.95 P=0.317 [0.86—1.05]
Interaction term	1.06 P=0.765 [0.71—1.58]	0.99 P=0.929 [0.83—1.19]

Notes: Model IV is the fully adjusted model controlling for all socio-demographic, health and behavioural covariates

Table S7. Estimates from Cox models with COPD interaction terms (N=4478)

	Model IV + interaction (COPD* living alone)	Model IV + interaction (COPD*disengagement)
Living alone	1.32 P=0.086 [1.96—1.81]	1.30 P=0.019 [1.04—1.61]
Low social contact	0.97 P=0.428 [0.88—1.05]	0.96 P=0.415 [0.88—1.05]
Social disengagement	1.24 P=0.000 [1.11—1.38]	1.17 P=0.034 [1.01—1.36]
Loneliness	0.95 P=0.380 [0.87—1.06]	0.96 P=0.382 [0.87—1.06]
Interaction term	0.98 P=0.935 [0.67—1.45]	1.10 P=0.304 [0.92—1.32]

Notes: Model IV is the fully adjusted model controlling for all socio-demographic, health and behavioural covariates

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