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Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2016;42:31–41
DOI: 10.1159/000447449
Accepted: June 3, 2016
Published online: August 19, 2016

Original Research Article

Geographical Variation in Dementia Mortality in Italy, New Zealand, and Chile: The Impact of Latitude, Vitamin D, and Air Pollution

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Key Words
Dementia · Alzheimer's disease · Geographical variation · Epidemiology

Abstract
Background: Dementia risk is reported as being higher in the north compared to the south, which may be related to vitamin D deficiency. If this were the case, an opposite gradient of risk would be observed in the southern hemisphere, but this has not been investigated previously. ***Methods:*** We calculated standardised mortality ratios (SMRs) for deaths in 2012 where dementia (Alzheimer's disease, vascular or unspecified dementia) was recorded as the underlying cause for 20 regions in Italy, 20 District Health Board areas in New Zealand and 29 Health Service areas in Chile. ***Results:*** Dementia SMRs were higher in northern than central or southern Italy. The inverse pattern was seen in women in New Zealand, with rates higher on South Island than North Island. However, dementia risk was raised in eight regions in the north and centre of Chile in both men and women. ***Conclusions:*** Geographical variation plays a key role in dementia risk, but patterns vary in men and women. In the northern hemisphere, dementia mortality is higher in the north, but the pattern in the southern hemisphere is more complex.

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Dement Geriatr Cogn Disord 2016;42:31–41
DOI: 10.1159/000447449

Introduction

Dementia is a major global public health issue, and the number of people affected is projected to increase dramatically in the future [1]. Alzheimer's disease remains the commonest cause of dementia, but many cases of dementia are of mixed aetiology, and there is evidence of substantial overlap in risk factors for vascular and neurodegenerative causes of dementia [2]. Preventing dementia from developing or delaying the onset of clinical symptoms would substantially reduce disease numbers [3]. However, the aetiology of dementia is not fully understood: known and unknown genetic factors and the commonest risk factors (diabetes, midlife hypertension and obesity, smoking, depression, cognitive inactivity, and low educational attainment) do not fully explain dementia risk [4, 5]. The geographical distribution of dementia cases is not random; several studies have reported higher rates in the north compared to the south in the northern hemisphere [6–12]. One suggested explanation for this gradient of risk by latitude is relative insufficiency of vitamin D related to sunlight exposure [13–17]. We hypothesised that if this mechanism does contribute to dementia risk, the opposite latitudinal gradient should be observed in southern hemisphere settings. However, we are unaware of any studies in the southern hemisphere. Thus, we present the first such analysis using publicly available mortality data to compare Italy, New Zealand, and Chile.

Methods

We obtained regional dementia mortality and population data from the Italian National Institute of Statistics (http://dati.istat.it/), the New Zealand Ministry of Health (http://www.health.govt.nz/), and the Chilean Ministry of Health (http://www.deis.cl/). Data for selected mortality outcomes in New Zealand are available through the Ministry of Health website, but age-specific dementia data were provided on request. We identified deaths where ICD-10 codes F01 and F03 (vascular and unspecified dementia) and G30 (Alzheimer's disease) were recorded as the underlying cause of death. The latest data available in Italy were from 2012 for the total population (all ages) of each of the 20 regions of Italy. New Zealand data covered all 20 District Health Boards in 2012; we selected the population aged 50 years or older and excluded Maori and Pacific peoples to ensure broad comparability between the populations in Italy and New Zealand. Chilean dementia data from 2012 were obtained for the total population of the 29 Health Service areas covering the whole country.

From these data we calculated standardised mortality ratios (SMRs) with accompanying 95% confidence intervals (CIs) for dementia in all regions of all three countries using the standard method [18]. SMRs were also calculated for Alzheimer's disease and vascular dementia where possible. These SMRs were then mapped in R for Windows version 3.2.3 using the ggplot2 package [19].

Results

From a total Italian population of 59 million (52% female) in 2012, there were 15,701 vascular or unspecified dementia deaths plus 10,823 Alzheimer's disease deaths (total for all dementias: 26,524). We found dementia SMRs to be increased in the north of Italy (men: 107, 95% CI 104–111; women: 115, 95% CI 113–117) and lower in the south (men: 79, 95% CI 75–83; women: 71, 95% CI 68–73) compared to the centre of the country (men: 103, 95% CI 98–108; women: 102, 95% CI 99–105) (fig. 1, table 1), but the pattern for Alzheimer's disease suggested an increased risk in the centre of Italy (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000447449).

Of 1.4 million non-Maori, non-Pacific peoples New Zealanders aged 50 years or older (52% female), 1,582 died with dementia in 2012 (including 529 with Alzheimer's disease and

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DOI: 10.1159/000447449

Table 1. Dementia SMRs (95% CIs) by region of Italy

Region	All dementias		Alzheimer's disease	
	men	women	men	women
North	107 (104–111)	115 (113–117)	93 (88–98)	101 (97–104)
Centre	103 (98–108)	102 (99–105)	118 (110–126)	117 (112–123)
South	79 (75–83)	71 (68–73)	92 (86–98)	84 (79–88)
Islands	110 (104–117)	97 (93–101)	115 (105–126)	101 (94–108)
North-West				
Piemonte	118 (110–127)	120 (115–126)	92 (81–104)	90 (83–99)
Valle d'Aosta/Vallée d'Aoste	101 (63–160)	179 (142–227)	155 (88–274)	163 (110–242)
Liguria	151 (136–169)	153 (142–164)	154 (131–182)	159 (143–178)
Lombardia	90 (85–95)	104 (100–108)	101 (93–109)	115 (110–122)
North-East				
Trentino-Alto Adige/Südtirol	88 (74–104)	102 (91–114)	90 (70–117)	85 (70–103)
Veneto	116 (109–125)	122 (116–128)	87 (77–98)	93 (85–101)
Friuli-Venezia Giulia	93 (80–109)	111 (101–122)	50 (37–70)	86 (72–102)
Emilia-Romagna	118 (110–127)	114 (108–120)	73 (63–84)	72 (65–80)
Centre				
Toscana	117 (108–127)	118 (112–125)	138 (124–155)	145 (135–157)
Umbria	125 (106–146)	124 (111–138)	144 (115–180)	121 (102–143)
Marche	147 (131–164)	133 (123–143)	142 (119–168)	135 (120–153)
Lazio	78 (72–84)	79 (75–84)	93 (83–104)	93 (86–100)
South				
Abruzzo	123 (108–140)	128 (117–139)	141 (117–170)	156 (138–177)
Molise	106 (80–142)	87 (70–108)	121 (80–182)	106 (77–144)
Campania	59 (54–64)	54 (51–57)	68 (59–77)	64 (58–70)
Puglia	89 (81–97)	78 (73–83)	108 (96–122)	99 (91–108)
Basilicata	89 (71–112)	63 (53–76)	110 (81–151)	75 (57–98)
Calabria	80 (70–91)	67 (61–74)	86 (70–104)	62 (52–72)
Islands				
Sicilia	104 (97–112)	89 (85–94)	109 (97–121)	88 (81–96)
Sardegna	128 (115–144)	121 (111–131)	136 (115–161)	138 (123–156)

332 with vascular dementia; the subtype was not specified for the remainder). There was little difference in SMR between North and South Islands in men (North Island: 101, 95% CI 92–111; South Island: 96, 95% CI 82–113), but in women dementia SMRs were higher on South Island than North Island (North Island: 95, 95% CI 89–102; South Island: 114, 95% CI 102–127) (fig. 2, table 2). However, these differences were not as clear for Alzheimer's disease (online suppl. fig. 2) or vascular dementia (online suppl. fig. 3).

Of 17.4 million people in Chile (51% female), there were 3,852 dementia deaths in 2012 (including 1,585 Alzheimer's disease deaths). Dementia SMRs were increased in the Norte Grande (men: 126, 95% CI 100–159; women: 130, 95% CI 112–169) and the Zona Central, which includes the Santiago Metropolitan Region (men: 105, 95% CI 99–112; women: 104, 95% CI 99–110) and were generally reduced elsewhere (fig. 3a, table 3). SMRs were even higher in the Santiago Metropolitan Region itself (men: 128, 95% CI 118–139; women: 114, 95% CI 108–125) (fig. 3b) than in the rest of the Zona Central. The observed pattern was less marked for Alzheimer's disease (table 3, online suppl. fig. 4), with no increase in SMRs in the Norte Grande, but SMRs remaining raised in the Santiago Metropolitan Region, particularly in men (men: 122, 95% CI 107–139; women: 109, 95% CI 100–126).

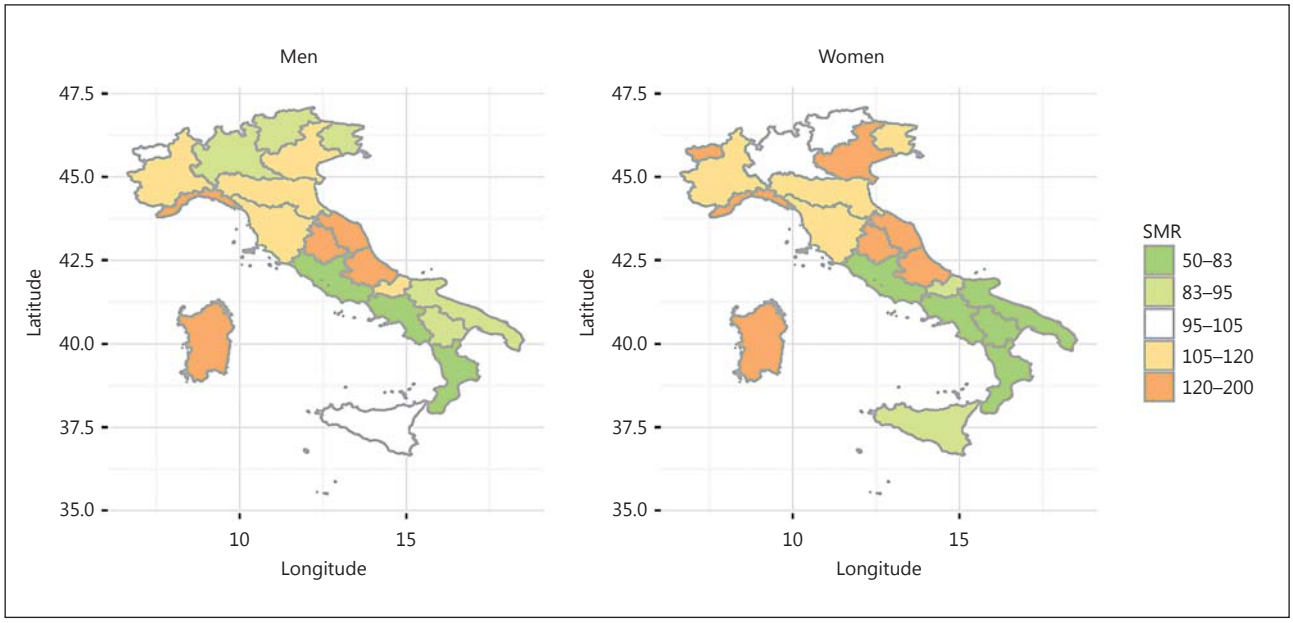

Fig. 1. Dementia SMRs by region of Italy for men and women.

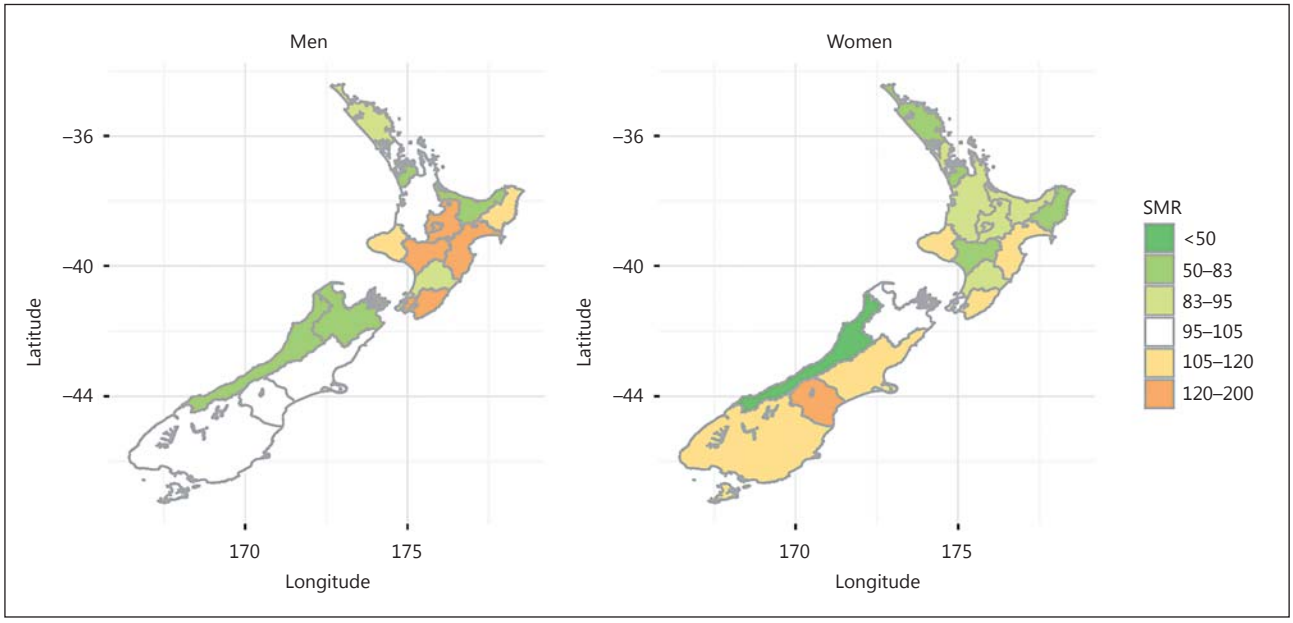

Fig. 2. Dementia SMRs by District Health Board of New Zealand for men and women (population aged 50 years and older).

Discussion

We found increased dementia SMRs in the north of Italy compared to the south, a possible inverse pattern in New Zealand – higher rates in the south compared to the north – at least in women, but increased SMRs in central and northern Chile.

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DOI: 10.1159/000447449

Table 2. Dementia SMRs (95% CIs) by District Health Board of New Zealand (population aged 50 years and older)

District Health Board	Men			Women		
	all dementias	AD	VD	all dementias	AD	VD
North Island	101 (92–111)	94 (79–112)	100 (82–121)	95 (89–102)	96 (85–109)	97 (82–115)
South Island	96 (82–113)	117 (90–153)	101 (73–140)	114 (102–127)	112 (92–136)	109 (82–143)
North Island						
Northland	90 (60–136)	124 (67–231)	48 (15–148)	73 (53–101)	80 (45–141)	73 (33–162)
Waitemata	104 (82–132)	86 (54–137)	92 (55–153)	94 (79–112)	76 (53–108)	120 (83–176)
Auckland	121 (94–156)	130 (84–201)	125 (75–207)	136 (115–161)	127 (92–174)	207 (148–289)
Counties Manukau	60 (43–85)	48 (24–96)	84 (47–152)	69 (55–87)	87 (60–126)	40 (19–83)
Waikato	102 (77–135)	78 (44–136)	108 (63–186)	95 (78–116)	114 (82–160)	49 (25–98)
Lakes	131 (83–208)	253 (140–457)	89 (29–275)	95 (65–139)	120 (65–223)	66 (21–203)
Bay of Plenty	78 (53–116)	79 (40–158)	63 (26–153)	92 (71–118)	81 (49–132)	83 (43–159)
Tairawhiti	116 (55–242)	157 (51–486)	134 (34–536)	58 (27–121)	135 (56–325)	–
Hawke's Bay	146 (104–205)	168 (95–295)	126 (60–264)	110 (83–144)	142 (91–219)	90 (43–189)
Taranaki	106 (66–170)	59 (19–183)	101 (38–269)	112 (81–155)	61 (28–137)	205 (114–370)
MidCentral	90 (59–138)	54 (20–145)	210 (119–369)	87 (64–118)	97 (58–165)	127 (68–236)
Whanganui	149 (88–251)	67 (17–269)	86 (22–345)	52 (28–97)	17 (2–122)	31 (4–223)
Capital and Coast	84 (58–122)	57 (26–127)	98 (49–195)	101 (80–128)	82 (51–132)	88 (47–164)
Hutt	138 (94–205)	140 (70–280)	90 (34–240)	102 (74–141)	100 (56–181)	83 (35–199)
Wairarapa	130 (68–249)	46 (6–324)	–	109 (66–182)	144 (65–321)	–
South Island						
Nelson Marlborough	74 (46–119)	83 (37–184)	53 (17–165)	100 (75–134)	73 (39–136)	107 (53–214)
West Coast	73 (27–194)	–	74 (10–525)	42 (16–113)	35 (5–247)	–
Canterbury	104 (82–131)	127 (87–185)	145 (97–216)	119 (102–139)	125 (95–165)	148 (105–208)
South Canterbury	104 (56–194)	132 (50–352)	42 (6–301)	153 (106–220)	104 (47–232)	158 (66–379)
Southern	97 (72–131)	132 (83–209)	75 (38–150)	112 (91–137)	121 (85–173)	50 (24–105)

AD = Alzheimer's disease; VD = vascular dementia.

Comparison with the Literature

Several studies have described higher rates of dementia in the north compared to the south of Finland, England, Sweden, Scotland, Newfoundland, and China [7–12]. However, to the best of our knowledge, nothing has previously been published on geographical variation in dementia rates in the southern hemisphere.

Limitations and Strengths

These analyses were based on publicly available mortality data and therefore have their limitations. Death certification is widely used in epidemiological studies to identify cases of dementia, though any mention of dementia on the death certificate is considered a better dependent variable than instances when dementia is recorded as the underlying cause of death, since many people with dementia die from something else [20, 21]. Although this methodology has previously been criticised [22], more recent studies suggest that dementia reporting on death certificates is improving and seems to be sufficiently robust for epidemiological purposes, see for example a false-negative rate of 18% in a memory clinic population [12, 20]. However, death certification probably remains less reliable in identifying dementia subtype; for example, while Alzheimer's disease is by far the commonest cause of dementia, in Italy the proportion of cases denoted as Alzheimer's disease ranged from 23 to 67% (median 45%), the figures in New Zealand were 0–71% (median 32%) and in Chile 11–59% (median 42%). Thus, the findings for dementia subtype must be interpreted in the light of this fact, and the differences in the patterns seen for all dementias may be related to the accuracy

Table 3. Dementia SMRs (95% CIs) by region of Chile

Region	All dementias		Alzheimer's disease	
	men	women	men	women
Natural region[1]				
Norte Grande	126 (100–159)	130 (112–169)	85 (55–132)	95 (72–143)
Norte Chico	56 (42–75)	77 (64–96)	54 (34–86)	78 (58–109)
Zona Central[2]	105 (99–112)	104 (99–110)	106 (96–116)	105 (98–116)
Zona Sur	86 (74–101)	77 (68–89)	98 (78–124)	79 (98–116)
Zona Austral	85 (50–143)	94 (66–152)	88 (39–195)	122 (74–257)
Santiago Metropolitan Region	128 (118–139)	114 (108–125)	122 (107–139)	109 (100–126)
Health Service area				
Arica	76 (42–137)	87 (59–127)	99 (45–221)	57 (27–119)
Iquique	145 (95–220)	131 (98–176)	95 (43–212)	150 (98–230)
Antofagasta	142 (104–196)	153 (124–188)	72 (36–144)	83 (54–129)
Atacama	32 (14–71)	106 (75–149)	38 (12–118)	116 (70–193)
Coquimbo	64 (47–88)	69 (55–86)	60 (36–99)	66 (46–95)
Valpo-SnAntonio	87 (63–120)	74 (58–94)	57 (31–106)	91 (64–127)
Viña-Quillota	79 (63–99)	97 (84–112)	105 (77–143)	101 (81–126)
Aconcagua	112 (76–166)	118 (89–156)	76 (36–160)	84 (50–141)
Metropolitana Norte	151 (119–191)	112 (95–133)	143 (98–208)	91 (68–122)
Metropolitana Occidental	131 (107–161)	94 (80–110)	149 (111–201)	115 (92–143)
Metropolitana Central	132 (106–165)	128 (111–147)	120 (83–173)	118 (94–149)
Metropolitana Ote	125 (106–149)	120 (108–132)	110 (83–146)	103 (87–123)
Metropolitana Sur	158 (133–189)	129 (114–146)	152 (115–202)	143 (120–172)
Metropolitana Sur Ote	93 (76–115)	96 (83–111)	83 (59–116)	81 (63–103)
O'Higgins	83 (65–107)	111 (93–132)	91 (62–132)	123 (95–158)
Maule	86 (68–109)	90 (75–107)	86 (60–124)	92 (70–121)
Ñuble	71 (48–103)	99 (78–126)	63 (34–117)	127 (91–176)
Concepción	108 (79–147)	85 (68–106)	136 (89–208)	106 (78–144)
Arauco	63 (32–127)	45 (23–86)	77 (29–204)	24 (6–96)
Talcahuano	77 (52–114)	66 (47–93)	97 (56–167)	84 (53–134)
Bío-Bío	50 (31–82)	61 (43–86)	76 (41–141)	85 (54–133)
Araucanía Norte	88 (55–140)	80 (55–115)	119 (64–221)	110 (68–180)
Araucanía Sur	92 (71–119)	75 (61–93)	125 (88–176)	78 (56–107)
Valdivia	119 (87–163)	77 (58–103)	89 (50–156)	77 (49–121)
Osorno	57 (32–103)	83 (59–118)	50 (19–134)	50 (25–101)
Reloncaví	78 (50–121)	92 (68–123)	103 (57–186)	128 (87–190)
Chiloé	46 (22–96)	42 (23–76)	32 (8–127)	–
Aisén	102 (46–227)	81 (42–155)	123 (40–380)	109 (45–262)
Magallanes	75 (38–151)	101 (66–155)	68 (22–211)	128 (71–231)

[1] Chile can be divided into five 'natural regions'. Since these include subregions, the following definitions were used. Norte Grande: Arica, Iquique, Antofagasta; Norte Chico: Atacama, Coquimbo; Zona Central: Valpo-SnAntonio, Viña-Quillota, Aconcagua, Metropolitana, O'Higgins, Maule, Ñuble, Concepción, Arauco, Talcahuano, Bío-Bío; Zona Sur: Araucanía, Valdivia, Osorno, Reloncaví, Chiloé; Zona Austral: Aisén, Magallanes.

[2] Including the Santiago Metropolitan Region.

of death certification rather than to factors relevant to specific illnesses. Also, accuracy of reporting may vary between countries.

Many people in the community with dementia are not formally diagnosed [23]. Since it is necessary to have a diagnosis for it to be recorded on a death certificate, it is possible that variation in diagnosis rates across a country could have influenced our findings. This is partic-

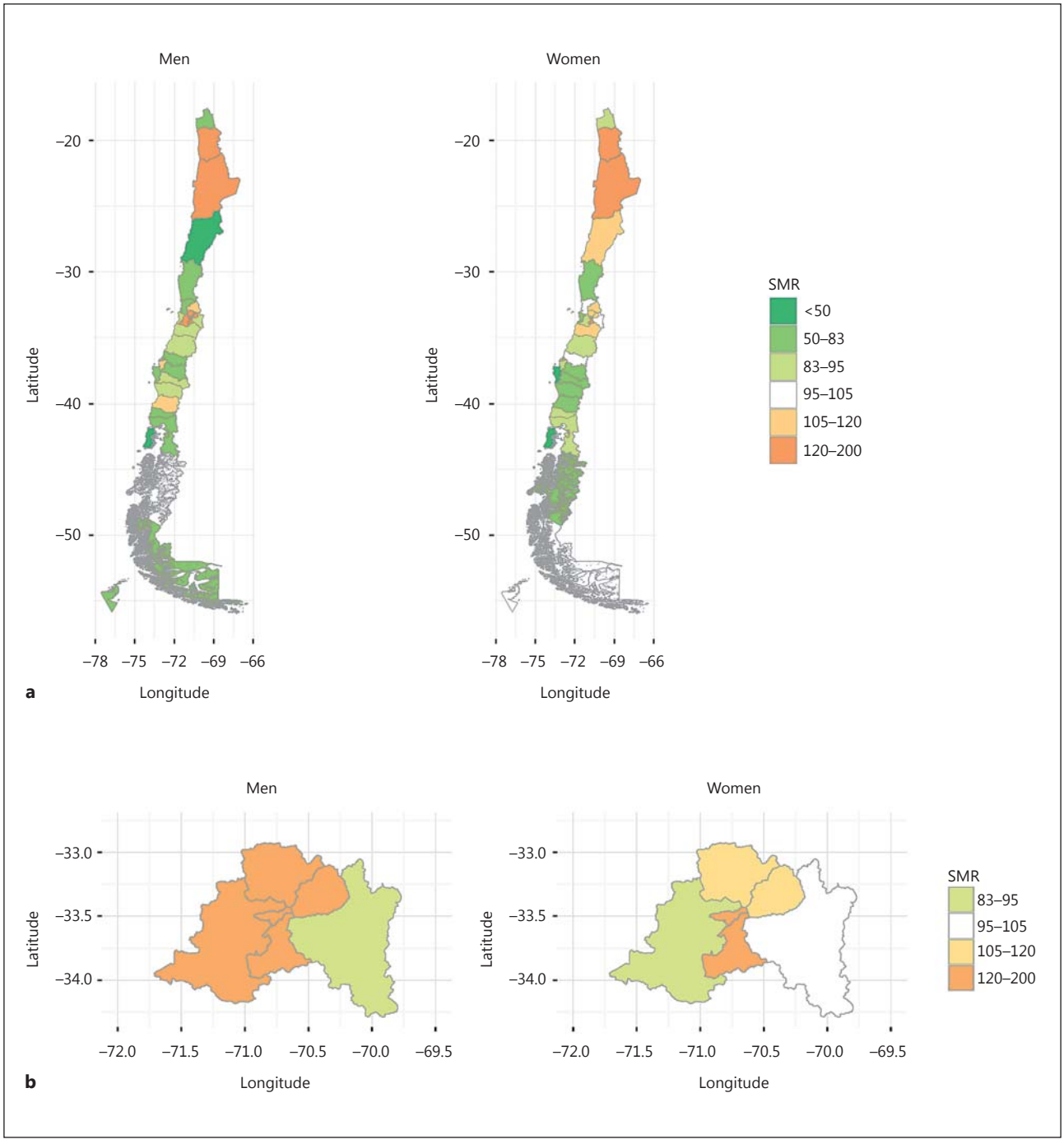

Fig. 3. a Dementia SMRs by Health Service area of Chile for men and women. **b** Dementia SMRs by Health Service area of Chile for men and women: Santiago Metropolitan Region.

ularly the case in countries such as Chile that have undergone rapid demographic change over the last two decades, requiring substantial adaptation by the health services. Indeed, a recent survey suggested that Chilean physicians generally have poor training in dementia [24]. Therefore, it is possible that the observed differences in dementia mortality between the south and the central region (i.e., the capital of Chile) could be partly explained by expertise

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DOI: 10.1159/000447449

of physicians in relation to dementia. Furthermore, there may be cultural differences in that individuals in some areas may not want the diagnosis of dementia to appear on their relative's death certificate. However, the consistent pattern seen in a number of different countries adds weight to the hypothesis that the observed geographical variation may represent a real effect. Moreover, it seems unlikely that the difference in mortality rate between the south and north of Chile, for example, could be explained solely by accuracy of death certification.

The data used included residential location at death, which may have biased our findings since the probability of being in residential care increases steeply in later life, leading to the danger of simply mapping the residential care facilities. However, the large areas used for each country are likely to have minimised this bias, as a large proportion of people would probably remain in the area in which they had previously lived. Furthermore, one previous study reported increased dementia mortality rates in those born on the north side of Bonavista Bay in Newfoundland compared to the south [9]. Another study in Scotland found no geographical variation in dementia rates based on county of school attended at age 11 years, but substantial variation based on residential location five or six decades later [12]. Birth records were accessed for a subsample and 79% had attended school in their county of birth.

Finally, as with all ecological studies, we should be cautious in inferring that these observed associations are causal or that they will still apply at the level of the individual. Nevertheless, accumulating evidence from numerous countries using different methodologies strongly suggests that our findings deserve further attention.

Possible Mechanisms

It was not been here to examine the effect of relevant covariables (education, socioeconomic status, etc.) on geographical variation in dementia rates. However, a twin study previously found that this substantial variation remained even after the removal of genetic and shared environmental variance, potentially implicating one or more unshared environmental factors [12]. One environmental risk factor in which there is growing interest is sunlight exposure (and consequently vitamin D levels) [13]. Four prospective studies including almost 17,000 individuals all found that lower vitamin D levels at baseline were associated with an increased risk of developing dementia [14–17]. Another prospective study found that people with vitamin D deficiency showed faster cognitive decline than individuals with sufficient levels [25]. Furthermore, a case-control study found an association between polymorphisms in the vitamin D receptor gene and the presence of Alzheimer's disease [26]. Our finding that dementia rates are higher in the north of the northern hemisphere would be consistent with the hypothesis that vitamin D – or other light-related mechanisms, for example UVB mobilisation of nitric oxide [27] or the potential relation between latitude and affect [28] – may be important in the pathogenesis of dementia. However, the evidence from the southern hemisphere is more mixed.

There are several ways in which vitamin D could be involved in the development of Alzheimer's disease, including neuroprotection, regulation of neurotrophic factors, its involvement in calcium homeostasis, and its effects on the immune system through cytokine regulation [29]. Our findings from the southern hemisphere might possibly be explained by higher mean serum concentrations of 25-hydroxyvitamin D in older adults in Chile (75.5 nmol/l) [30] and New Zealand (general population 60.5–65.1 nmol/l) [31] compared to Italy (37.9 nmol/l) [32]. For example, if vitamin D had a neuroprotective effect, higher mean levels in the population could diminish the effect of variation in serum levels with latitude on dementia risk. A national survey from New Zealand found higher mean levels of vitamin D in the northern region compared to central and southern regions, but no difference in prevalence of vitamin D deficiency between the three regions after adjusting for age, sex, and ethnic group [31].

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There are also alternative mechanisms which may explain part of the reported patterns. For example, the increased dementia risk in the Santiago Metropolitan Region may be related to air pollution, many aspects of which – nitrogen oxides, carbon monoxide, particulate matter (PM_{10} and $PM_{2.5}$), and ozone – have been related to dementia risk [33–35]. There is further supporting evidence from another large metropolitan area: a recent study found a biomarker which has been proposed for Alzheimer's disease [36] (reduced cerebrospinal fluid levels of $A\beta_{1-42}$) in children from Mexico City who had been exposed to high levels of air pollution in utero and throughout their life compared to controls [37]. Other mechanisms are also possible, for example a high cancer risk was identified in Antofagasta in the north of Chile in relation to historical high levels of arsenic in drinking water, demonstrating that environmental exposures can have long-lasting effects on health [38].

There is evidence for geographical stratification of genetic heritage, at least in Scotland [39]. Similarly, the proportion of people carrying the *APOE* ε4 allele is higher in northern Europe than southern Europe, which may explain some of the observed variation in dementia risk [40]. Excluding Maori and Pacific peoples from our New Zealand analyses should have ensured broad comparability in terms of genetic heritage with Italy; a similar process was not possible for Chile, which may partially explain the differing results. However, a twin study in Sweden showed geographical variation in dementia risk of a similar size in monozygotic twins discordant for dementia, implying that whatever the explanation for this finding is, it cannot be solely genetic [12].

Finally, as mentioned above, a further possible mechanism relates to affective disorders. Both psychological distress and depression have been linked with dementia risk [41, 42]. Psychiatric disorder has been shown to vary by region in Chile, with a high incidence of depression in Tarapacá and Metropolitana, regions with raised dementia SMRs in the present study [43].

Conclusions

We found increased dementia SMRs in the north of Italy compared to the south, consistent with similar studies from across the northern hemisphere. In New Zealand and Chile, we saw a more complex pattern, with some evidence of an inverse pattern, in women at least, in New Zealand and an increased risk in some northern areas of Chile. Further, more detailed work examining the epidemiology of dementia in the southern hemisphere is needed, but these findings add weight to the hypothesis that dementia risk varies with geography (and probably latitude). We have also proposed two plausible environmental risk factors which may explain our findings: sunlight (and vitamin D) and air pollution.

Acknowledgements

The authors are grateful to Chris Lewis, Information Analyst from the New Zealand Ministry of Health, for providing the mortality data for New Zealand.

T.C. Russ and J.M. Starr are members of both the Alzheimer Scotland Dementia Research Centre funded by Alzheimer Scotland and the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross-council Lifelong Health and Wellbeing Initiative (G0700704/84698). Funding by the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, and Medical Research Council is gratefully acknowledged for the latter. T.C. Russ is supported by Alzheimer Scotland through the Marjorie MacBeath fellowship. A. Slachevsky is supported by CONICYT/FONDAP/15150012.

This work was supported by Alzheimer Scotland (charity).

Disclosure Statement

The authors have no conflicts of interest to declare. All of them are independent of the funders, who played no role in this study.

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