bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Centenarian Hotspots in Denmark

Anne Vinkel Hansen[1,2*], Laust Hvas Mortensen[1,2], Rudi Westendorp[1,2,3]

[1] Statistics Denmark, Denmark

[2] Department of Public Health, University of Copenhagen, Denmark

[3] Center for Healthy Aging, University of Copenhagen, Denmark

* Corresponding author: Statistics Denmark, Sejerøgade 11, 2100 København Ø, Denmark, email: *aih@dst.dk*, telephone: +45 39175083

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Abstract

Background: The study of regions with high prevalence of centenarians is motivated by a desire to find determinants of healthy ageing. While existing research has focused on selected candidate geographical regions, we explore the existence of hotspots in the whole the Denmark, which is a small and homogeneous country.

Methods: We performed a Kulldorff spatial scan across the whole of Denmark, searching for regions of birth, and regions of residence at age 71, where a significantly increased percentage of the cohort born 1906-1915 became centenarians. Next we compared mortality hazards for the identified regions to the rest of the country by sex and residence at age 71.

Results: We found a birth hotspot of 222 centenarians, 1.37 times more than the expected number, centered on a group of fairly remote rural islands. Significantly lower mortality hazards from age 71 onwards were confined to those who were born within the hotspot and persisted over a period of at least 30 years. At age 71, we found two residence-based hotspots of 348 respectively 238 centenarians, equaling 1.46- and 1.44 times the expected number. One is located in the high-income suburbs of the Danish capital and here the lower mortality hazard was confined to those who moved into the hotspot. In the second residence-based hotspot, both those who were born, and those who moved into the hotspot, showed significant lower mortality hazards.

Conclusion: Within the whole of Denmark, we identified several centenarian hotspots that have different biological underpinnings. These outcomes point to complex gene-environmental interactions explaining a variety of longevity trajectories.

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Introduction

Those who reach a hundred years capture our imagination. While the specific number is an arbitrary marker, becoming a centenarian is not a meaningless indicator of longevity, and the interest in geographical regions with high prevalence of centenarians has been ongoing at least since the start of the 20th century (Poulain et al 2013). The first of the current generation of well-validated longevity regions is the Sardinian "blue zone" (Poulain et al 2004), a small group of villages with a particularly high concentration of centenarians per 1000 births from 1880 to 1900. Other "blue zones" have been identified in the Okinawa region in Japan (Willcox et al 2008), the Ikaria island in Greece (Panagiotakos et al 2010) and the Nicoya peninsula in Costa Rica (Rosero-Bixby et al 2013). So far, the known longevity hotspots are in isolated, economically disadvantaged regions.

A plethora of explanatory factors has been proposed, roughly separating into seeing any effect as either genetic, rooted in local culture, or caused by local physical environment. For high-longevity zones in Calabria, Italy, areas with high prevalence of centenarians have been noted to also have a low variety of surnames, hinting at an explanation grounded in inbreeding (Montesanto et al 2007). Topographic factors, particularly altitude and steepness of terrain have been suggested (Pes et al.2013). Life style factors have been investigated with varying results - the population of the Nicoya region have a diet rich in fibres, proteins and trans fats (Rosero-Bixby et al 2013), while Okinawa is the only blue zone to have a significantly lower caloric intake than the reference population (Willcox et al 2007). For the Nicoya blue zone, it has been observed that the effect is exclusive to those born and resident in the Nicoya region, with a non-significant decrease in mortality among immigrants and no decrease in mortality among out-migrants. This hints at the effect being, in some way, one of physical environment, or at least not tied to cultural factors carried along by out-migrants. As places change over time (sanitation improves, public transportation replaces walking, pesticide use changes), exposure to a place may mean different things in different decades. To our knowledge, there has not been any exploration of whether the effects observed in the various blue zones persist in generations after the ones they were detected in.

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

In terms of longevity, Denmark is a curious case. The country is small, socially homogeneous, highly economically developed, and has one of the world's most generous universal welfare systems. At the same time, Denmark also has considerable social inequalities in health and a comparatively modest life expectancy, which is on par with that of the US. This study explores whether centenarian hotspots based on place of birth and place of residence late in life exist in Denmark. We explore the effects of time by examining whether such hotspots also prolong life in those moving there at a later age, and whether the effects remain in subsequent generations.

Methods

We constructed a cohort of men and women born in Denmark from 1906 to 1915 and still alive at the age of 71 (after the introduction of the civil registration system in 1968). For each person, we identified parish of birth and place of residence by age 71 plus data on date of death and emigration. The data source was the national registry in which full follow-up for change of residence, death and emigration is possible for all Danish residents since 1968 (Pedersen 2011). Place of birth is recorded for all persons alive and resident in Denmark from 1977 and onwards. Information on later-life socioeconomic position and marital status was sourced from the 1970 census.

We searched for clusters of centenarians using a Kulldorf spatial scan (Kulldorf 1997) as implemented in the R package SpatialEpi. For each parish, the number of centenarians and the expected number based on number of births by sex and year of birth were assigned to the geographical centroid of the parish. The method then constructed zones as circular areas containing up to a pre-specified proportion (we chose to set this to 5 %) of the total population. For each zone, a likelihood ratio test statistic was constructed assuming a Poisson distribution of the number of observed centenarians. The zone most likely to be a cluster was selected as the one maximizing the test statistic, and significance measures were computed by Monte Carlo simulation. Any other zones for which the test statistic was significant at the pre-specified significance level (set to 0.05) were flagged as secondary clusters.

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Having detected a hotspot, we compared mortality and centenarian proportion in people born inside and outside the hotspot for men and women. Mortality was compared via hazard ratios computed by Cox regression. We also compared mortality and centenarian proportion according to whether the subjects were born and stayed in, had left, were born outside and had moved to, or were born and had stayed in the cluster by age 71.

In order to explore the extent to which the effect was stable over time, we compared cohort mortality for those born inside and outside the cluster over the period from 1978 to 2015 for the cohorts with birth years 1906-1915, 1916-1925 and 1926-1935. Five-year mortality rate ratios were computed by Poisson regression.

As a sensitivity analysis, since a large percentage of observations were coded with municipality rather than parish of birth, we performed cluster detection where the observations coded with municipality were weighted out across the parishes whose centroids were inside that municipality. The weights were proportional to the size of the birth cohort by year and sex in each parish.

We also performed cluster detection based not on the proportion of a birth cohort reaching age 100, but on the proportion of those resident in a region by age 71 who become centenarians.

Analyses were done using R version 3.2.3 software.

Results

There were 740,927 live births in Denmark from 1906 to 1915 (Statistics Denmark). Of these, we found 425,791 still alive and resident in Denmark by age 71. In order to make analyses by geographic location of birth, we made exclusions as follows: Those emigrating between age 71 and 100 (n = 1107), those lost in registry (n = 829), those with no parish of birth recorded (n = 57,178) and those missing information on parish of residence by age 71 (n=4,596). Of the group missing parish of birth, the majority (n = 42,436) had

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

a record of municipality of birth in place of parish. Of the 362,064 individuals remaining in the study, 4,739 (1.3 %) reached the age of 100.

We first examined hotspots by parish of birth. This yielded one hotspot centered on a group of fairly remote rural islands (Langeland and encompassing rural areas on the islands of Funen and Lolland – see Figure 1). The birth hotspot had a total of 222 centenarians, 1.37 times the expected number, and the proportion was significantly larger than that of the remaining country with a p-value of 0.03. Per table 1, those born in the birth hotspot did not differ markedly from the baseline population on socioeconomic factors, except in being more likely to be homeowners (67 % vs 59 %).

Mortality differences between those born inside and outside the birth hotspot were more pronounced for women (HR 0.93, 95% CI 0.91 – 0.95) than for men (HR 0.97, 95% CI 0.95 – 1.00). This corresponds to the proportion surviving from 71 to 100 being 2.8 % and 1.9 % inside and outside the birth hotspot for women, and 0.6 % and 0.5 % for men (table 2).

Mortality for those born in the birth hotspot and still remaining there by age 71 was slightly lower than for those who have left the birth hotspot (HR when compared to those born and remaining outside the hotspot 0.94, 95 % CI 0.92 - 0.97 and 0.96, 95 % CI 0.94 – 0.98 respectively) but with overlapping confidence intervals. There was no decrease in mortality for those born outside the birth hotspot but had moved into the birth hotspot by age 71 (HR 0.99, 95 % CI 0.96 – 1.03). The centenarian proportions reflect this pattern: the proportion surviving to 100 is 1.3% for those born outside and 1.8% for those born inside the birth hotspot, wherever they live by age 71.

Age-specific mortality rates for the cohorts born in the birth hotspot in the periods 1916-25 and 1926-35 are shown in the supplementary table. Age-specific mortality rates were comparable across birth cohorts, and remain significantly lower than expected from age 86 and onwards.

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

The sensitivity analysis including the group coded with municipality rather than parish of birth in the cluster detection process found the same primary hotspot, with 240 centenarian cases, 1.33 times the expected number with a p-value of 0.10.

When scanning for centenarian hotspots by place of residence at age 71 (see figure 2), we found one primary hotspot with 1.39 times (p-value 0.001), and one secondary hotspot with 1.33 times (p-value 0.003) the expected number of centenarians. The primary residence hotspot consisted of parishes in generally high-income suburbs in Northern Zealand. The secondary residence hotspot covered a region in Mid-Jutland. The total number of centenarians in each region was 379 and 337, respectively, for the primary and secondary residence hotspots. There were no further secondary clusters.

Inhabitants of the primary residence hotspot in Northern Zealand showed a higher proportion with a high socioeconomic position (26 % in the two highest groups, compared to 10 % for the cohort in general) and a higher proportion of divorcees (Table 3) whereas no such differences were observed for the secondary residence hotspot in Mid-Jutland.

Table 4 presents the matching mortality hazards for the residence-based hotspot from age 71 onwards. Within the primary hotspot, i.e. the high-income suburbs of the Danish capital, the significant lower mortality hazards were confined to those who moved into the hotspot (HR 0.88, 95 % CI 0.87 – 0.90), whereas those who were born in the same region did not show any benefit, irrespective whether they stayed or left the region (1.00, 95 % CI 0.96 – 1.04 and 1.00, 95 % CI 0.96 – 1.05 respectively). In the second residence-based hotspot, those who moved into the hotspot, showed significant lower mortality hazards (0.96, 95 % CI 0.93 – 0.98) but this was not different when compared to those who were born and stayed in the same region (0.95, 95 % CI 0.92 – 0.97).

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Discussion

We found a Danish longevity birth hotspot centered on a group of fairly remote rural islands, with a 1.37 times increased chance of becoming a centenarian for the cohort born there 1906-1915. The effect is reflected in a lower post-71 mortality for both men and women, although the effect is markedly stronger in women. Mortality is lower for all those born in the hotspot, whether or not they have left by age 71. The difference in mortality is still observable and not substantially weakened for women born in the hotspot 1916-25 and 1926-35. We find two regions with significantly increased probabilities of reaching age 100 for those resident there at age 71, both with centenarian rates similar to those of the birth hotspot.

The main strength of this study is that the use of routinely collected, nation-wide registry data allows us to explore longevity distribution across an entire country for a 10-year birth cohort, that we have full follow-up from at least the age of 71, and that we can examine the effect in subsequent birth cohorts. One weakness is that we only have follow-up from 1977 and thus are unable to examine the extent to which our effects are shaped by mortality or emigration earlier in life. We only measure place of residence at two points in life, although people may have moved in and out of the regions studied. The Kulldorff cluster detection method is known to be conservative (Thomas et al 2003), and is constructed for point data, not area-aggregated data as we used. A likely effect of aggregation is over-estimation of cluster sizes (Jones & Kulldorff 2012), which, in turn, would reduce the estimate of the hotspot with centenarianism. The method allows for hotspots that group together regions separated by sea – this may seem counterintuitive, but arguably, a short stretch of sea is not necessarily a boundary in terms of local culture, population mixing or socioeconomic factors.

Nearly 10 % of observations were excluded due to missing information on parish of birth. When those with municipality of birth recorded were included, the location of the primary hotspot did not change, and while the effect size decreased past the point of insignificance, the absolute change was only from a ratio of 1.37 to a ratio of 1.33.

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

The absolute centenarian proportions in the study are not large. Comparison between studies are complicated by different outcome measures and especially different study periods, but the relative increase in probability of becoming a centenarian of 37 % can be compared to the 50 % increase in probability for the Sardinian blue zone or the three-fold increase in probability for the Sardinian restricted blue zone. Similarly, the age 70-100 death rate ratio of 0.95 for the Langeland hotspot compared to the rest of Denmark compares to the death rate ratio of 0.8 for Nicoyan men. Given the relatively high geographic, economic and cultural homogeneity in Denmark, it is not surprising that relative differences in centenarian proportions within Denmark are moderate.

Whatever the causes of the observed increases in extreme longevity for those born in birth hotspot, they seem to be determined before age 71. We see comparable post-71 mortality estimates for those born and staying in and leaving the hotspot, and no decrease in mortality for those moving to the birth hotspot as compared to those born and remaining outside the hotspot. The fact that there seems to be no benefits to moving to the birth hotspot later in life is reinforced by the results of the analysis of hotspots based residence at age 71 – the best place to be born is not the best place to grow old. This could point to the causes of the increase in centenarian prevalence being genetic or related to early life exposures, or being rooted in behaviors that are learned before old age and continued after leaving the region. The analyses of the subsequent cohorts suggest that whatever the determinants of longevity in the birth hotspot, they remain a factor over a period of at least 30 years.

When looking for causes for the birth hotspot, we should note that this area historically has been a poor area with an agricultural economy dominated by large estates. The main island of Langeland experienced mass emigration for a period leading up to the birth of the cohort studied - 30% of the population emigrated in the period 1868-1909 as compared to a national average of 10 % (Bender). While blue zones are generally poor and rural areas, this may be a rare case of those left behind by emigration being the healthier group, i.e. an ‘unhealthy migrant-effect’. Denmark is typically not considered a country with large

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

genetic variation, but although the Danish population has historically been relatively mobile and there are no strong geographical barriers to mobility, there is still a tendency for surnames to cluster geographically, perhaps indicating lower mobility than might generally be the narrative (Boldsen 1992).

The interpretation of the residence at age 71 hotspots is less straightforward than that of the birth hotspot, given the nature of migration. Place of residence at age 71 is an indicator of socioeconomic and health status, and thus a straightforward interpretation of the secondary hotspots as "the best places to grow old" is not possible. They can just as well be interpreted as "the places where the fittest live by age 71". Certainly, the Northern Zealand residential hotspot has markedly higher socioeconomic position by 1970 than the cohort in general and there could plausibly be selection factors into the Mid-Jutland hotspot as well.

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

References

Bender, Henning. “Kilder på nettet til udvandringen fra Danmark”. Retrieved from http://henningbender.dk/uf/80000_89999/85186/4957b29e11c812f8411c0b076a8c61a1.pdf

Boldsen, Jesper L. "Geographical distribution of some Danish surnames: Reflections of social and natural selection." Journal of biosocial science 24.04 (1992): 505-513.

Jones, Stephen G., and Martin Kulldorff. "Influence of spatial resolution on space-time disease cluster detection." PLoS One 7.10 (2012): e48036.

Kulldorff, Martin. "A spatial scan statistic." Communications in Statistics-Theory and methods 26.6 (1997): 1481-1496.

Montesanto, A., et al. "Spatial analysis and surname analysis: complementary tools for shedding light on human longevity patterns." Annals of human genetics 72.2 (2008): 253-260.

Panagiotakos, Demosthenes B., et al. "Sociodemographic and lifestyle statistics of oldest old people (> 80 years) living in ikaria island: the ikaria study." Cardiology research and practice 2011 (2011).

Pedersen Pedersen, Carsten Bøcker. "The Danish civil registration system." *Scandinavian journal of public health* 39.7_suppl (2011): 22-25.

Pes, Giovanni Mario, et al. "Lifestyle and nutrition related to male longevity in Sardinia: an ecological study." Nutrition, Metabolism and Cardiovascular Diseases 23.3 (2013): 212-219.

Poulain, Michel, et al. "Identification of a geographic area characterized by extreme longevity in the Sardinia island: the AKEA study." Experimental gerontology 39.9 (2004): 1423-1429.

Poulain, Michel, Anne Herm, and Gianni Pes. "The Blue Zones: areas of exceptional longevity around the world." Vienna Yearbook of Population Research (2013): 87-108.

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Rosero-Bixby, Luis, William H. Dow, and David H. Rehkopf. "The Nicoya region of Costa Rica: a high longevity island for elderly males." Vienna yearbook of population research/Vienna Institute of Demography, Austrian Academy of Sciences 11 (2013): 109.

Statistics Denmark: “HISB3: Summary Vital Statistics.” Retrieved from www.statbank.dk/HISB3

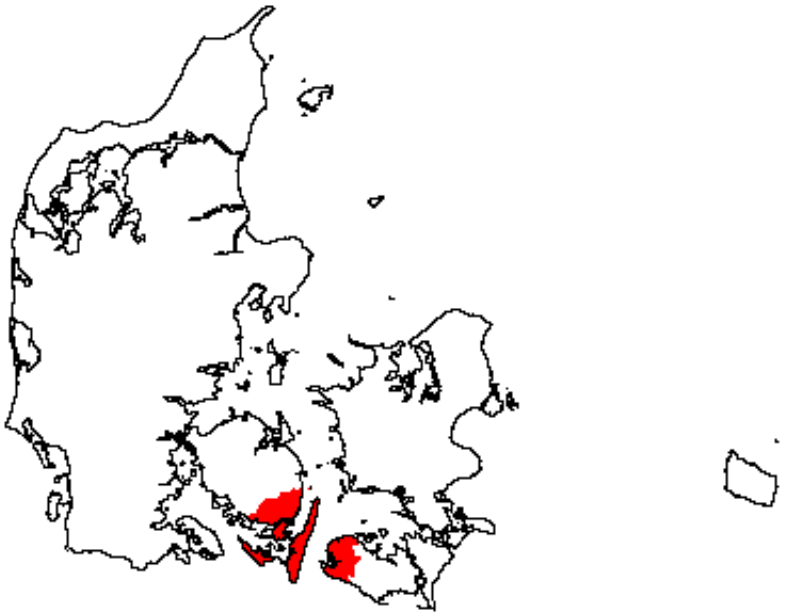
J Thomas, Avis, and Bradley P Carlin. "Late detection of breast and colorectal cancer in Minnesota counties: an application of spatial smoothing and clustering." Statistics in Medicine 22.1 (2003): 113-127.

Willcox, Bradley J., et al. "Caloric restriction, the traditional Okinawan diet, and healthy aging." Annals of the New York Academy of Sciences 1114.1 (2007): 434-455.

Willcox, D. Craig, et al. "They really are that old: a validation study of centenarian prevalence in Okinawa." The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 63.4 (2008): 338-349.

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Figure 1: Hotspot for proportion of birth cohort surviving from 71 to 100.



	Number of parishes included	Population	Proportion of total population	Expected number of cases	Observed number of cases	Ratio	p-value
Langeland hotspot	70	12,472	3.4	161.9	222	1.37	0.03

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Table 1: Socio-economic characteristics at age 71 for the study population and the birth-cohort centenarian hotspot

	Study population		Birth-cohort hotspot	
	N	**%**	**N**	**%**
Sex				
Female	198,034	54.7	6,773	54.3
Male	164,030	45.3	5,699	45.7
Socioeconomic position in 1970				
1 (highest)	14,169	3.9	476	3.8
2	22,739	6.3	763	6.1
3	93,278	25.8	3,164	25.4
4	65,195	18	2,035	16.3
5 (lowest)	89,038	24.6	3,285	26.3
Pensioner	70,348	19.4	2,471	19.8
Other/unknown	7,297	2	278	2.2
Marital status in 1970				
Unknown	2,049	0.6	61	0.5
Divorced	18,750	5.2	547	4.4
Married	270,997	74.8	9,377	75.2
Unmarried	31,898	8.8	1,175	9.4
Widow(er)	38,370	10.6	1,312	10.5
Homeowner in 1970				
No	147,632	40.8	4,156	33.3
Yes	214,432	59.2	8,316	66.7

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

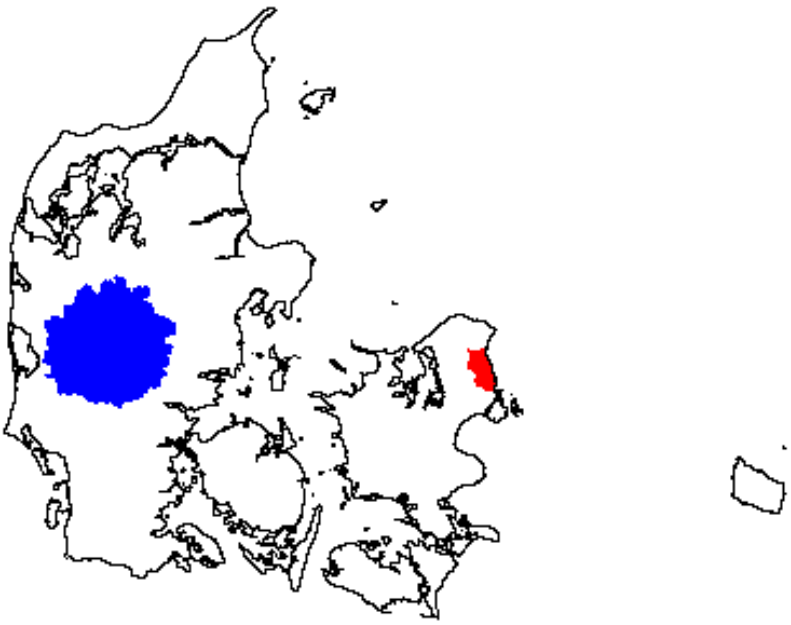
Table 2: Mortality and centenarian proportion for those born in and outside the birth cohort centenarian hotspot, by sex and by place of residence at age 71. HR computed by Cox regression.

	N	Alive by age 100, % (95 % CI)	HR (95% CI)	Adjusted* HR (95% CI)
Hotspot				
Born outside hotspot	349,592	1.3 (1.3 - 1.3)	1 (REF)	1 (REF)
Born in hotspot	12,472	1.8 (1.6 - 2.0)	0.95 (0.93 – 0.97)	0.95 (0.94 – 0.97)
Sex				
Men born outside hotspot	158,331	0.5 (0.5 - 0.5)	1 (REF)	1 (REF)
Men born in hotspot	5,699	0.6 (0.4 - 0.9)	0.97 (0.95 – 1.00)	0.98 (0.96 1.01)
Women born outside hotspot	191,261	1.9 (1.9-2.0)	1 (REF)	1 (REF)
Women born in hotspot	6,773	2.8 (2.4 – 3.2)	0.93 (0.91 – 0.95)	0.94 (0.91 – 0.96)
Place of birth and residence at age 71				
Born and stayed outside hotspot	346,230	1.3 (1.3 - 1.3)	1 (REF)	1 (REF)
Born outside and moved to hotspot	3,362	1.3 (1 - 1.8)	0.99 (0.96 – 1.03)	1.01 (0.97 – 1.04)
Born in and left hotspot	6,652	1.8 (1.5 - 2.2)	0.96 (0.94 – 0.98)	0.96 (0.93 – 0.98)
Born and stayed in hotspot	5,820	1.8 (1.4 - 2.1)	0.94 (0.92 – 0.97)	0.95 (0.92 – 0.97)

*Adjusted for birth year, socioeconomic position, marital status and homeownership.

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Figure 2: Primary (red) and secondary (blue) hotspots for proportion of residents in a region at age 71 surviving to age 100



	Number of parishes included	Population	Proportion of total population	Expected number of cases	Observed number of cases	Ratio	p-value
Primary hotspot	30	17,676	4.9	238.8	348	1.46	0.001
Secondary hotspot	72	13,133	3.6	165.6	238	1.44	0.001

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Table 3: Socio-economic characteristics at age 71 for the study population and the residence-based centenarian hotspots

	Study population		Primary residence-based hotspot		Secondary residence-based hotspot	
	N	%	N	%	N	%
Sex						
Female	198,034	54.7	10,096	57.1	6,725	51.2
Male	164,030	45.3	7,580	42.9	6,408	48.8
Socioeconomic position in 1970						
1 (highest)	14,169	3.9	2,157	12.2	469	3.6
2	22,739	6.3	2,422	13.7	751	5.7
3	93,278	25.8	4,870	27.6	3,798	28.9
4	65,195	18.0	3,062	17.3	2,063	15.7
5 (lowest)	89,038	24.6	2,433	13.8	3,376	25.7
Pensioner	70,348	19.4	2,311	13.1	2,441	18.6
Other/unknown	7,297	2	421	2.4	235	1.8
Marital status in 1970						
Divorced	18,750	5.2	1,374	7.8	305	2.3
Married	270,997	74.8	12,999	73.5	10,323	78.6
Unmarried	31,898	8.8	1,403	7.9	1,282	9.8
Widow(er)	38,370	10.6	1,794	10.1	1,160	8.8
Unknown	2,049	0.6	106	0.6	63	0.5
Homeowner in 1970						
No	147,632	40.8	9,186	52	2,483	18.9
Yes	214,432	59.2	8,490	48	10,650	81.1

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Table 4: Mortality and centenarian proportion for those born in and outside the residence-based centenarian hotspots, by sex and by place of residence at age 71. HR computed by Cox regression.

	N	Alive by age 100, % (95 % CI)	HR (95% CI)	Adjusted* HR (95% CI)
Hotspots				
Resident outside hotspots	331,255	1.3 (1.2 - 1.3)	1 (REF)	1 (REF)
Primary hotspot	17,676	2.0 (1.8 - 2.2)	0.89 (0.88 – 0.91)	0.91 (0.89 – 0.93)
Secondary hotspot	13,133	1.8 (1.6 - 2.1)	0.95 (0.93 – 0.96)	0.96 (0.95 – 0.98)
Sex				
Men resident outside hotspots	150,042	0.5 (0.4 - 0.5)	1 (REF)	1 (REF)
Men in primary hotspot	7,580	0.8 (0.6 - 1.0)	0.91 (0.89 – 0.93)	0.94 (0.92 – 0.97)
Men in secondary hotspot	6,408	0.9 (0.7 - 1.1)	0.92 (0.90 – 0.94)	0.94 (0.92 – 0.96)
Women resident outside hotspots	181,213	1.9 (1.8 - 2.0)	1 (REF)	1 (REF)
Women in primary hotspot	10,096	2.9 (2.6 - 3.2)	0.90 (0.88 – 0.92)	0.92 (0.90 0.94)
Women in secondary hotspot	6,725	2.7 (2.3 - 3.1)	0.94 (0.92 – 0.97)	0.96 (0.94 – 0.99)
Movement out of and into primary hotspot				
Born and stayed outside hotspot	341,707	1.3 (1.2 - 1.3)	1 (REF)	1 (REF)
Born outside and moved to hotspot	15,610	2.0 (1.8 - 2.3)	0.88 (0.87 – 0.90)	0.90 (0.89 – 0.92)
Born in and left hotspot	2,681	1.1 (0.8 - 1.6)	1.00 (0.96 – 1.04)	1.00 (0.96 – 1.03)
Born and stayed in hotspot	2,066	1.5 (1.1 - 2.1)	1.00 (0.96 – 1.05)	1.00 (0.96 – 1.05)
Movement out of and into secondary hotspot				
Born and stayed outside hotspot	340,103	1.3 (1.2 - 1.3)	1 (REF)	1 (REF)
Born outside and moved to hotspot	5,473	2.0 (1.6 - 2.4)	0.96 (0.93 – 0.98)	0.97 (0.95 – 1.00)
Born in and left hotspot	8,828	1.4 (1.2 - 1.7)	0.95 (0.92 – 0.96)	0.95 (0.93 – 0.97)
Born and stayed in hotspot	7,660	1.7 (1.4 - 2.0)	0.95 (0.92 – 0.97)	0.96 (0.94 – 0.98)

*Adjusted for birth year, socioeconomic position, marital status and homeownership.

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Supplementary material

Table S1: Parishes included in the birth cohort centenarian hotspot

Cluster	Parishes included
Primary	Arninge, Avnede, Bjerreby, Branderslev, Bregninge, Bregninge, Brudager, Bøstrup, Dannemare, Drejø, Egense, Ellested, Fodslette, Frørup, Fuglsbølle, Gislev, Græshave, Gudbjerg, Gudme, Gurreby, Halsted, Hesselager, Horslunde, Hov, Humble, Hundstrup, Kappel, Kirkeby, Krarup, Kværndrup, Købelev, Landet, Langå, Lindelse, Longelse, Lunde, Magleby, Marstal, Nakskov, Nordlunde, Ollerup, Omø, Oure, Rise, Rudkøbing, Sandby, Sankt Jørgens, Sankt Nikolaj, Simmerbølle, Skovlænge, Skrøbelev, Skårup, Snøde, Stenstrup, Stoense, Stormark, Strynø, Svindinge, Sørup, Thurø, Tillitse, Tranderup, Tranekær, Tryggelev, Tullebølle, Tved, Ulbølle, Utterslev, Vejstrup, Vestenskov, Vester Skerninge, Vester Åby, Vesterborg, Vindeby, Vor Frue, Ærøskøbing, Øksendrup, Ørbæk, Øster Skerninge, Åstrup

Table S2: Parishes included in the primary and secondary residence-based centenarian hotspots

Cluster	Parishes included
Primary	Bagsværd, Birkerød, Bistrup, Blovstrød, Buddinge, Christians, Dyssegård, Gammel Holte, Gentofte, Hellerup, Helleruplund, Hørsholm, Jægersborg, Karlebo, Kongens Lyngby, Lundtofte, Maglegårds, Ny Holte, Nærum, Ordrup, Rungsted, Skovshoved, Sorgenfri, Stengård, Søborggård, Søllerød, Tårbæk, Vangede, Vedbæk, Virum
Secondary	Arnborg, Assing, Aulum, Blåhøj, Bording, Brande, Brejning, Bryrup, Bølling, Egvad, Ejstrup, Engesvang, Faster, Filskov, Fredens, Funder, Gadbjerg, Give, Givskud, Gjellerup, Grene, Grindsted, Grove, Grædstrup, Hammer, Hanning, Havnstrup, Hedeager, Herborg, Herning, Hoven, Hvejsel, Ikast, Ilskov, Karup, Klovborg, Kragelund, Lindeballe, Linnerup, Nørre Snede, Nørre Vium, Nøvling, Oddum, Rind, Ringive, Sankt Johannes, Simmelkær, Sinding, Skarrild, Skjern, Snejbjerg, Studsgård, Sunds, Sædding, Sønder Borris, Sønder Felding, Sønder Omme, Them, Thorning, Thyregod, Timring, Tjørring, Tyrsting, Tørring, Vester, Videbæk, Vildbjerg, Vorgod, Vrads, Ølgod, Ørre, Øster Nykirke

bioRxiv preprint doi: https://doi.org/10.1101/170654; this version posted August 9, 2017. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Table S2: Mortality rate ratios comparing the birth cohort centenarian hotspot to the rest of Denmark, for the cohorts born 1906-15, 1916-25 and 1926-35

	Birth year		
	1906-1915	**1916-1925**	**1926-1935**
	Mortality rate ratio (95 % CI)	**Mortality rate ratio (95 % CI)**	**Mortality rate ratio (95 % CI)**
Population age 71, n	362,064	367,269	339,258
Born in hotspot, n	12,472	12,365	10,559
Age 71-75	0.98 (0.94 - 1.02)	0.94 (0.90 - 0.98)	1.00 (0.95 - 1.05)
Age 76-80	0.98 (0.95 - 1.02)	0.91 (0.88 - 0.95)	0.98 (0.93 - 1.02)
Age 81-85	0.94 (0.90 - 0.97)	0.94 (0.91 - 0.98)	
Age 86-90	0.95 (0.91 - 0.98)	0.94 (0.90 - 0.98)	
Age 90-95	0.92 (0.87 - 0.97)		
Age 96-100	0.91 (0.84 - 0.99)		