Chapter 8

Causes of Death Among 9000 Danish Centenarians and Semisuper-Centenarians in the 1970–2012 Period

Lasse Kaalby, Axel Skytthe, Karen Andersen-Ranberg, and Bernard Jeune

8.1 Introduction

The prevalence of morbidity and disability is very high among centenarians (Andersen-Ranberg et al. 2001a). As most centenarians suffer from several diseases (multi-morbidity) they are at high risk of dying – but what do they die of? This question has scarcely been examined. The few existing studies on causes of death (CoD) are often based on selected samples of centenarians.

According to the World Health Organization's recommendations, death certificates should always single out one "main cause of death," also known as the *underlying* CoD. This is the disease or injury that initiated the events leading to death, but not the *immediate* CoD. It is common among older people for co-existing chronic conditions to contribute to death, without being part of the sequential pathway from the underlying to the immediate CoD. These conditions are called *contributing* CoDs. All three types of CoD are listed on the death certificate form if they are known, but only the underlying CoD is registered as the main CoD.

The existing studies on CoD can be divided into two categories: autopsy studies and register studies.

L. Kaalby · A. Skytthe · K. Andersen-Ranberg
Syddansk Universitet, Odense, Denmark
e-mail: lkm@rsyd.dk; askytthe@health.sdu.dk; karanberg@health.sdu.dk

B. Jeune (✉)
University of Southern Denmark, Odense, Denmark
e-mail: BJeune@health.sdu.dk

8.2 Autopsy Studies

The earliest studies were autopsy studies. Ishii and Sternby (1978a, b, c) published three articles based on the findings of 23 hospitalized Japanese centenarians. The most common underlying causes of death among this group were identified as cerebro- and cardiovascular disease (CVD) and pneumonia. All of these cases displayed signs of atherosclerosis, and myocardial fibrosis was present in 15 of the 23 centenarians. In six of the 23 centenarians, malignant neoplasms were found, although these appeared to be a contributing CoD rather than the underlying cause.

John and Koelmeyer (2001) is an autopsy study of cases from a forensic department in New Zealand of 319 nonagenarians and centenarians (with a mean age of 92) who were registered as having died suddenly between 1988 and 1998. Of the 319 deaths, 272 (85%) were from natural causes, while 47 (15%) were from unnatural causes. The most common causes of natural death were ischemic heart disease (23%), bronchopneumonia (12%), acute myocardial infarction (8%), cerebrovascular accidents (6%), ruptured aneurism (5%), and gastrointestinal disease (5%), including bleeding. CVD accounted for 50% of the deaths. However, cancer was listed as the underlying CoD in only six cases, and as a contributing cause of death in five additional cases. Among the subjects who died of unnatural causes, falls accounted for 35 of the 47 deaths, and suicides accounted for three deaths. Only 13 cases (5%) were “written off” as being attributable to “old age or senile debility.” The authors concluded “that elderly die of disease not of old age.”

Berzlanovich et al. (2005) also examined autopsy reports from a forensic department in Austria on 40 centenarians who died unexpectedly in Vienna between 1985 and 2002 (a total of 842 centenarians died in Vienna over this period). All of the deaths were from sudden natural causes, and occurred in private homes. The most common underlying CoD among these centenarians was CVD, which was found in 27 (68%) of the cases. Of these CVD deaths, 15 (38%) were from acute myocardial infarction, six (15%) were from acute cardiac failure, and six (15%) were from a rupture of an aortic aneurysm. Pneumonia was the underlying CoD in 10% of the cases, and gastrointestinal disease was the underlying CoD in 5% of the cases. Advanced neoplastic disease with widespread metastases was found in three of the cases. The autopsies also revealed that many of these centenarians had suffered from preexisting conditions that were not the underlying CoD, but that were probably contributory.

The most extensive study of autopsies of centenarians examined the autopsy reports on almost all of the centenarians who died in one Italian province over a certain period (Motta et al. 2010). These 140 autopsy reports were compared with autopsy reports on 96 younger old adults (aged 75–95). The study presented evidence on the frequency of various pathologies, but without clearly stating whether these pathologies were causes of death. Most of the pathologies of the circulatory system occurred more frequently among the centenarians than among the younger older people. The pathologies that occurred most frequently among the centenarians were ischemic cardiac diseases (37.8% versus 33.3%) and cerebral ischemia (23.4% versus 17.0%), followed by severe arteriosclerosis (18.4% versus 3.5%) and pulmonary embolism (11.3% versus 8.9%). In contrast, acute myocardial infarction

occurred less frequently among the centenarians (5.9%) than among the younger older individuals (20.5%), and was only rarely identified as the underlying cause of death. Interestingly, cardiac amyloidosis was found among 11.3% of the centenarians, but among none among the younger older people. Respiratory pathologies were also very common among centenarians and higher than among the younger older people; especially chest infection (40.4% versus 24.8%), but also chronic obstructive pulmonary disease (8.4% versus 3.5%). However, the most remarkable finding was that the frequency of non-skin cancer was much lower among the centenarians than among the younger older people (16.3% versus 39.0%). Moreover, among those with cancer, the frequency of metastases was much lower among the centenarians than among the younger older individuals (26% versus 55%).

8.3 Register Studies

One of the earliest register studies on CoD among centenarians is included in a study on Finnish centenarians (Louhija 1995). Of the population of 92 deceased centenarians studied, 36% died from circulatory diseases, 34% died from diseases of the respiratory system, and 21% died from another CoD. Only 3% died from neoplasms.

A comprehensive register study of 35,867 deceased English centenarians examined the CoD and the place of death between 2001 and 2010. This study by Evans et al. (2014) found that the most common underlying CoD was pneumonia (17.7%), followed by cerebrovascular diseases (10%), ischemic heart disease (8.6%), and other circulatory diseases (9.8%). Cancer was cited as the underlying CoD in only 4.4% of these cases. A very large share of these deaths was attributed to “old age” (28.1%). This CoD was more common among deaths that occurred in a nursing home (34.2%), a residential home (35.9%), or the individual’s home (35.5%) than among deaths that occurred in a hospital (9.7%). The study compared the CoDs of the centenarians to the CoDs of individuals aged 80–99 years, and found that the centenarians died more frequently from pneumonia and “old age,” and less frequently from CVD and cancer.

A systematic review by Pavlidis et al. (2012) included 16 articles on cancer as the CoD among centenarians published over a time span of more than 80 years (1918–2002). The authors concluded that cancer was rarely an underlying CoD among centenarians, and that when it was reported as an underlying CoD, the immediate CoD was rarely due to the spread of tumors, but to cancer-related complications, such as bleeding from stomach cancer or pneumonia in patients with lung cancer. The authors stressed that the cases of cancer observed among centenarians were at a lower stage with fewer metastases than among younger old people.

In summary, the most common CoDs among centenarians appear to be circulatory and respiratory diseases. While “old age” was frequently mentioned as the only CoD in some studies, this cause was seldom cited in autopsy studies, and even less often in studies based on cases from forensic departments. Moreover, in autopsy studies cancer was not cited as a common CoD.

It is, however, difficult to evaluate whether centenarians – and especially semi-supercentenarians (aged 105–109) – die of one underlying clearly diagnosed disease or of a combination of equally important diseases (multi-morbidity), or whether a proportion of centenarians die of “old age” (i.e., of a breakdown of multiple systems of the body).

In this study, we examine the causes of death (CoD) of almost 9000 Danish centenarian deaths, including almost 500 semi-supercentenarians. We examine the relative frequencies of the CoDs and the age-, gender- and cause-specific mortality rates, and whether these rates have changed over the decades since 1970. We compare the CoDs of centenarians with the CoDs of people aged 85–99, and the CoDs of semi-supercentenarians with the CoDs of centenarians in the same periods.

8.4 Methods and Materials

8.4.1 Data Collection

The material includes all individuals who died in Denmark between 1970 and 2012 aged ≥ 100 . For comparison, data have been extracted on people who died at ages 85–99 in the same period.

All of the data are from The Danish Register of Causes of Death (DRCD) and the Civil Registration System (CRS). The DRCD collects information on all deaths in Denmark. The registry, which contains data from 1970 onward, is managed by the Danish Health Data Authority (DHDA). The CoDs are classified using ICD – 8 in the 1970–1993 period, and using ICD-10 from 1994 onward (Table 8.1). To overcome the differences in coding schemes over time, the CoDs have been grouped into 49 categories by the DHDA (Sundhedsstyrelsen 2002). In addition, existing information on autopsies was obtained. After the law on autopsies was changed in 1990, there was a substantial decline in the number of ordinary autopsies performed in Denmark. As a result, the presented data are almost solely based on information given by the physicians who filled in the death certificates.

A total of 8573 centenarian deaths registered between 1970 and 2012 were obtained from the DRCD. In addition, 1019 centenarians were identified as alive and living in Denmark as of January 1, 2013, based on data obtained from the CRS registry in 2015. As there is a 3-year delay in the release of data by the DRCD, the last year that could be included for analyses of cause-specific mortality was 2012.

Aggregated data on 85–99-year-olds were collected from Statistics Denmark. Statistics on cause-specific mortality are available in 5-year age groups up to ages 80–84, but the statistics for higher ages are available only for the broader age group 85+. The collected data are based on the categorization of the 49 CoDs that is also used in the DRCD. By subtracting the number of deaths among centenarians from the number of deaths in the age group 85+, the number of deaths among the 85–99-year-olds in each of the 49 categories was calculated.

Table 8.1 Cause of death categorization using ICD-10 and ICD-8

Cause of Death	ICD-10	ICD-8
Ischemic heart disease	I20-I25	410-414
Cerebro-vascular disease	I60-I69	430-438
Other cardiovascular disease	I10-I15, I27, I30-I52, I28, I70- I79	400-404,420-429,440-448
Pneumonia	J13-J18	480-486
Other respiratory disease	J00-J06, J10-J11, J20-J22, J30- J47, J60-J99	460-474, 490-493,500-519
Cancer	C00-C34, C37-C97, D00-D09	140-199, 200-209
Digestive diseases	K00-K31, K70-K83, K35-67, K85- K93	520-577
Urinary & genital disease	N00-N08, N20-N23, N10-N19, N25-N99	580-629
Endocrine disorders	E00-E07, E10-E90	240-246, 250-279
Mental disease	F00-F99	290-315
Ill-defined conditions/ senility	R00-R99	780-796
Accidents	V01-V99, W00-X59, Y40-Y86, Y87.1-87.2	800-807, 810-823, 825-949
Other	A00-A09, A20-A99, B00-B90, B99,A15-19, D10-D48, D50-89, G00-G99, H00-H95, I00-I09, I26, I80-I99, O00-O99, L00-L99, M00-M99, Q20-Q28, Q00-Q18, Q30-Q99, P00-P86, X60-X84, Y87.0, X85-Y36	000-019, 210-239, 280-289, 320-398, 450- 458, 630-678, 680-738, 740-779, 950-999

8.4.2 Data Analysis

The data analysis of cause-specific mortality in this study is based on the 8573 deaths of centenarians from 1970 to 2012 extracted from the DRCD. Of the 8573 deaths, 14 had missing information about the CoD, which leaves 8559 deaths to be examined.

We have reduced the 49 categories to 13 groups of CoDs based on a combination of the relative frequencies (at least 1.5% of all deaths) and the absolute mortality rate in the last period of 2010–2012 (at least 10 deaths per 1000 person-years). The CoDs within the 49 categories that in relative and absolute numbers were below these thresholds have been grouped in the category “other causes of death.” The classification is displayed in Table 8.1.

Since the data on cause-specific mortality among individuals aged 85 and older were only available in aggregated form, we were only able to calculate

cause-specific mortality among 85–99-year-olds as a single age group. We were therefore unable to calculate standardized mortality rates.

Age-, gender-, and cause-specific mortality rates for centenarians were estimated based on individual data. In the comparison with the 85–99-year-olds, the aggregated data were used to estimate the cause-specific mortality rates.

The Danish certificate of death follows WHO’s recommendations, and consists of two parts. In the first part, the physician provides a sequential list of conditions leading to the immediate CoD. The underlying CoD – i.e., the disease or injury that initiated the events leading to death – is listed last. In the second part of the certificate, the physician can report any other significant disease that contributed to the death (contributing CoD). In this study, we focus only on the underlying CoD.

8.5 Results

The number of centenarian deaths in Denmark has increased from 535 in 1970–1979 to 3165 in 2000–2009. A total of 8559 deaths were registered during 1970–2012 (see Table 8.2). The median age at death among Danish centenarians has increased to above 101 years due to a decrease in the proportion of deaths among 100- and 101-year-olds and an increase in deaths among those aged 102 or older. In particular, the proportion of centenarians who died at age 105 or older doubled over the study period (from 3.6% in the 1970s to 6.2% in 2010–2012). Furthermore, the gender distribution changed over time in favor of the female population: 82.9% of the centenarians who died in 2010–2012 were women, up from 68.6% in the 1970s.

Table 8.3 shows that in the last period (2010–2012), CVD – a category that includes ischemic heart diseases, cerebrovascular diseases, and other cardiovascular diseases – was listed as the underling CoD in about one-third of the deaths. However, this proportion has been declining substantially since the 1970s, when CVD was

Table 8.2 Age and gender of 8559 deceased Danish centenarians between 1970 and 2012

	1970–1979		1980–1989		1990–1999		2000–2009		2010–2012		Total
	n	Percent	n	Percent	n	Percent	n	Percent	n	Percent	N
Gender											
Women	367	68.6	895	73.0	1713	77.8	2684	84.8	1186	82.9	6845
Men	168	31.4	331	27.0	489	22.2	481	15.2	245	17.1	1714
Age											
100	237	44.3	524	42.7	924	42.0	1259	39.8	577	40.3	3521
101	148	27.7	290	23.7	570	25.9	805	25.4	350	24.5	2163
102	69	12.9	193	15.7	341	15.5	484	15.3	215	15.0	1302
103	42	7.9	103	8.4	177	8.0	290	9.2	129	9.0	741
104	20	3.7	71	5.8	82	3.7	165	5.2	71	5.0	409
105+	19	3.6	45	3.7	108	4.9	162	5.1	89	6.2	423
Total	535	100	1226	100	2202	100	3165	100	1431	100	8559

Table 8.3 Cause of death in 8559 centenarians by period of time

Cause of Death	1970–1979		1980–1989		1990–1999		2000–2009		2010–2012		Total	
	n	Percent	n	Percent	n	Percent	n	Percent	n	Percent	N	Percent
Ischemic heart disease	210	39.3	395	32.2	512	23.3	509	16.1	165	11.5	1791	20.9
Cerebro-vascular disease	57	10.7	98	8.0	148	6.7	215	6.8	91	6.4	609	7.1
Other cardiovascular disease	104	19.4	231	18.8	403	18.3	512	16.2	214	15.0	1464	17.1
Pneumonia	49	9.2	128	10.4	183	8.3	294	9.3	125	8.7	779	9.1
Other respiratory disease	16	3.0	49	4.0	55	2.5	67	2.1	33	2.3	220	2.6
Cancer	16	3.0	49	4.0	62	2.8	105	3.3	57	4.0	289	3.4
Digestive disease	7	1.3	14	1.1	50	2.3	82	2.6	42	2.9	195	2.3
Urinary & genital disease	6	1.1	8	0.7	22	1.0	71	2.2	33	2.3	140	1.6
Endocrine disease	0	0.0	6	0.5	20	0.9	124	3.9	39	2.7	189	2.2
Mental disease	6	1.1	17	1.4	49	2.2	147	4.6	103	7.2	322	3.8
Ill-defined conditions/senility	33	6.2	156	12.7	523	23.8	767	24.2	401	28.0	1880	22.0
Accidents	20	3.7	52	4.2	121	5.5	128	4.0	42	2.9	363	4.2
Other	11	2.1	23	1.9	54	2.5	144	4.6	86	6.0	318	3.7

identified as the underlying cause of death for more than two-thirds of centenarian deaths. This decline is mainly explained by a decline in the share of deaths from ischemic heart diseases, which declined by more than two-thirds. By contrast, the proportion of deaths in which cerebrovascular disease was identified as the underlying CoD decreased by only about one-third, while the shares of deaths from other types of CVD fell by one-quarter.

In contrast, the proportion of deaths for which pneumonia and other respiratory diseases was listed as the underlying CoD has been almost constant over time (at about 11–12%). The low proportions of deaths from cancer (about 3–4%) and from accidents (about 3–5%) were also constant, while the shares of deaths from most of the other minor groups of diseases increased. Deaths from mental diseases, including dementia, increased from about 1% to about 7%. Over the same period, deaths from ill-defined conditions/senility increased from about 6% to 28%, making this category the largest of the groups of underlying CoDs. In two-thirds of the deaths attributed to this group of causes, senility (“old age”) was listed as the underlying CoD; and it is this subgroup in particular that has grown over time.

Table 8.4 shows that the proportions for most underlying CoDs were lower among the semi-supercentenarians (aged 105–109) than among the individuals aged 100–104, and that a very low proportion of deaths among the semi-supercentenarians was from cancer (about 2%). Shares of deaths from other respiratory diseases (including COPD) and accidents (including falls) were slightly higher among the semi-supercentenarians, and were especially high for ill-defined conditions/senility: one-third of deaths among the semi-supercentenarians were attributed to this cause, compared to less than one-fifth of deaths among the individuals aged 100–104. In particular, deaths attributed to the subgroup senility (“old age”) increased sharply with age.

It is evident from Table 8.5, which shows the cause-specific mortality rates per 1000 person-years, that CVD was the leading underlying CoD in all periods, and especially in the 1970s and the 1980s. The absolute decline over time was substantial and steady for ischemic heart disease, with the share of deaths from this cause falling to almost one-quarter in 2010–2012 from very high levels in the 1970s (from 202.7 to 60.0 deaths per 1000 person-years). Over the same period, the decline in the share of deaths from cerebrovascular diseases and other cardiovascular diseases was much smaller.

Similarly, the mortality rate for pneumonia stayed constant at a relatively high level over the study period. Since the 1980s, the mortality rate for pneumonia was higher than the mortality rate for cerebrovascular diseases. The mortality rate for cancer stayed constant over this period, but at a relatively low level (less than half the rate for pneumonia). Except for accidents, the cause-specific mortality rates increased over the period for all other disease groups, especially for mental diseases, which increased sixfold; and for ill-defined conditions/senility, which increased fivefold. These increases resulted in a mortality rate in the 2000s of more than 10 per 1000 person-years for all of the defined groups of diseases.

It appears that centenarian women had a lower risk of dying from ischemic heart disease than centenarian men (see Table 8.6): the mortality rate for this cause was

Table 8.4 Cause of death in 8559 centenarians by age

Cause of Death	100		101		102		103		104		105+	
	n	Percent	n	Percent	n	Percent	n	Percent	n	Percent	n	Percent
Ischemic heart disease	775	22.0	432	20.0	262	20.1	167	22.5	81	19.8	74	17.5
Cerebro-vascular disease	247	7.0	169	7.8	89	6.8	55	7.4	24	5.9	25	5.9
Other cardiovascular disease	603	17.1	381	17.6	228	17.5	110	14.8	79	19.3	63	14.9
Pneumonia	326	9.3	190	8.8	129	9.9	66	8.9	31	7.6	37	8.8
Other respiratory disease	87	2.5	48	2.2	35	2.7	21	2.8	14	3.4	15	3.5
Cancer	128	3.6	76	3.5	40	3.1	19	2.6	17	4.2	9	2.1
Digestive disease	93	2.6	52	2.4	29	2.2	12	1.6	7	1.7	2	0.5
Urinary & genital disease	60	1.7	27	1.3	28	2.2	14	1.9	7	1.7	4	0.9
Endocrine disease	76	2.2	45	2.1	30	2.3	23	3.1	10	2.4	5	1.2
Mental disease	151	4.3	88	4.1	40	3.1	22	3.0	10	2.4	11	2.6
Ill-defined conditions/senility	678	19.3	487	22.5	303	23.3	176	23.8	100	24.4	136	32.2
Accidents	155	4.4	88	4.1	49	3.8	30	4.1	14	3.4	27	6.4
Other	142	4.0	80	3.7	40	3.1	26	3.5	15	3.7	15	3.5
Total	3521	100	2163	100	1302	100	741	100	409	100	423	100

Table 8.5 Cause-specific mortality rates per 1000 person-years (95% CI) by period

	1970–1979		1980–1989		1990–1999		2000–2009		2010–2012	
Cause of Death	MR	95% CI	MR	95% CI	MR	95% CI	MR	95% CI	MR	95% CI
Ischemic heart disease	203	177–232	179	156–190	125	115–136	80	73–87	60	52–70
Cerebro-vascular disease	55	43–72	43	35–52	36	31–42	34	30–39	33	27–41
Other cardiovascular disease	101	83–122	101	88–114	98	89–108	80	74–87	77	68–89
Pneumonia	48	36–63	56	47–66	45	39–52	47	42–52	47	40–56
Other respiratory disease	16	10–25	21	15–28	13	10–18	10	8–13	10	7–14
Cancer	16	10–25	21	16–28	15	12–19	16	14–20	21	16–27
Digestive disease	7	3–14	6	4–10	12	9–16	13	10–16	15	11–21
Urinary & genital disease	6	3–13	4	-8	5	3–8	11	9–14	12	9–16
Endocrine disease	0		3	1–6	5	3–6	19	16–23	14	10–19
Mental disease	6	3–13	7	5–12	12	9–16	23	20–27	37	31–45
Ill-defined conditions/senility	32	23–45	68	58–79	128	117–139	120	112–129	146	132–161
Accidents	19	13–30	23	17–30	30	25–35	20	17–24	15	11–21
Other	11	6–19	10	7–15	13	10–17	22	19–26	31	25–39

Table 8.6 Cause of death and gender-specific mortality rates per 1000 person-years (95% CI)

	Women		Men	
Cause of Death	MR	95% CI	MR	95% CI
Ischemic heart disease	103	97–108	132	120–146
Cerebro-vascular disease	37	34–40	36	30–44
Other cardiovascular disease	88	83–93	89	78–100
Pneumonia	43	39–46	69	61–79
Other respiratory disease	11	9–13	21	16–27
Cancer	16	14–18	25	20–31
Digestive disease	12	10–14	12	8–16
Urinary & genital disease	8	6–9	12	9–17
Endocrine disease	12	10–14	11	8–15
Mental disease	21	19–23	13	10–18
Ill-defined conditions/senility	116	110–122	103	92–115
Accidents	21	19–24	26	20–32
Other	19	17–22	20	15–25

102.6 per 1000 person-years for women versus 132.2 per 1000 person-years for men. The mortality rate for pneumonia and other respiratory diseases as the underlying CoD was lower among women than among men (for pneumonia: 42.7 versus 69.2 per 1000 person-years). The same pattern can be observed for the mortality

rate for cancer (15.8 versus 24.8 per 1000 person-years). On the other hand, the mortality rate for ill-defined conditions/senility as the main cause of death was a little higher among women than among men (115.8 versus 103.0 per 1000 person-years), and this pattern can also be seen for mental diseases (20.8 per versus 13.3 per 1000 person-years).

The proportion of individuals who died from ischemic heart disease was at the same level and decreased at the same rate over time among the centenarians as among the 85–99-year-olds (Fig. 8.1). Among both the 85–99-year-olds and the centenarians, ischemic heart disease was the leading CoD in the 1970s and the 1980s, but the share of deaths from this cause decreased from almost 40% to about 10% over the study period. However, the proportion of deaths from the group of cerebrovascular diseases was lower among the centenarians after the 1970s because the share decreased over time among the centenarians, but not among the 85–99-year-olds. The proportion of deaths from the group of other CVDs was a little higher for the centenarians in the most recent periods.

The proportion of deaths for which pneumonia was reported as the underlying CoD was higher among the centenarians than among the younger old people after the 1970s; over the study period, the share remained stable among the centenarians, but was halved among the younger old people (from about 10% to 5%). The share of deaths for which cancer was reported as the CoD was much lower among the centenarians (3–4%) than among the younger old people, for whom the share remained almost unchanged at around 15%. The share of deaths for which mental disease was the underlying CoD increased in both age groups over the period, but

Fig. 8.1 Cause of death among Danish younger old people and centenarians 1970–2012

rose slightly more among the younger age group (to about 10%). However, the proportion of deaths from ill-defined conditions/senility was much higher among the centenarians: by the end of the study period, the share was three times higher among the centenarians than among the younger age group. In contrast, the proportions of deaths from the remaining groups of reported CoDs were higher among the younger old people than among the centenarians, and increased more over time.

8.6 Discussion

In 2010–2012, CVD was the underlying CoD in about one-third of all deaths among centenarians. This represents a significant decline from the 1970s, when CVD was the underlying cause for up to two-thirds of all deaths. The proportion of deaths for which pneumonia or another respiratory disease was the underlying CoD remained almost constant in the 1970–2012 period (at about 12%). The proportion of deaths for which cancer was the underlying CoD was low and remained constant at about 3–4%. Except for accidents, the shares of deaths assigned to other CoD groups increased substantially over time: a sevenfold increase was observed for deaths from mental disease, and an almost fivefold increase was observed for deaths from ill-defined conditions/senility (reaching 28% in the last period). The cause-specific mortality rates confirm these trends.

The mortality rates for ill-defined conditions/senility and mental disease were higher among women than among men. The proportions of deaths for which other CVDs, pneumonia, and ill-defined conditions/senility were reported as the underlying CoD were higher among the centenarians than among the 85–99-year-olds, but the proportions of deaths from other causes, especially cancer, were lower among the older than the younger age group. The proportions of deaths from most of the underlying CoD groups were lower among the semi-supercentenarians (aged 105–109) than among the 100–104-year-old centenarians. But over the study period, ill-defined conditions/senility accounted for one-third of the underlying CoDs among the semi-supercentenarians, but less than one-fifth of the underlying CoDs among the 100–104-year-old centenarians.

8.6.1 *Cerebro- and Cardiovascular Diseases (CVD)*

Our finding that the mortality rates and the proportions of deaths from CVD were high even in the latest period are consistent with the findings from previous studies (Berzlanovich et al. 2005; Motta et al. 2010). This was the case for ischemic heart disease in particular, as of the three CVD groups of causes of death, this group was the largest from 1970 to the 2000s. However, after 2000 the largest group of causes of death was other cardiovascular diseases, including arteriosclerosis, hypertension, peripheral artery disease, and other heart diseases such as heart valve diseases. For

this group of underlying CoDs, both the relative proportion and the mortality rate decreased only moderately over time. The proportion of deaths for which cerebrovascular disease was the underlying CoD was smaller, and declined substantially over the period. We found that this group of causes accounted for 7% of deaths. Thus, our estimate is between previous estimates presented in Louhija (1995) (5%) and in Evans et al. (2014) (10%).

It is possible that the number of deaths due to CVD was underreported, as it has been shown that cardiovascular diseases are substantially underreported among living Danish centenarians (Andersen-Ranberg et al. 2013). As the proportion of the centenarians whose deaths were attributed to ill-defined conditions/senility is high in our study, especially for the most recent periods, a substantial number these deaths may have actually been caused by an undetected cardiovascular disease. A higher diagnostic threshold in very frail centenarians, as well as ageism, could explain such misreporting. It is therefore possible that CVD is still the cause of more than half of all centenarian deaths.

8.6.2 *Pneumonia and Other Respiratory Diseases*

The almost constant mortality rate for pneumonia over the 42-year study period is interesting, as the increasing number of centenarians might include more frail centenarians, and thus centenarians who are more susceptible to infections. The proportion of deaths from pneumonia (about one-tenth) in our study is consistent with the findings of other studies (Louhija 1995, Berzlanovich et al. 2005). In the relatively large autopsy study by Motta et al. (2010), the frequency of chest infection was shown to be much higher (40.4%). However, this was the frequency of all infection pathologies found in the lungs of the Italian centenarians during autopsies. It is likely that these infections represented the underlying CoD in only a fraction of these cases.

In the recent register study of centenarian deaths in England by Evans et al. (2014), the proportion of deaths from pneumonia was also found to be higher (17.7%). This result might be attributable to the fact that the share of the English centenarians studied who died in hospital was twice as high as the share of the Danish centenarians in our sample (27% versus 13%), and that pneumonia was more likely to have been listed as the underlying CoD among those who died in English hospitals.

Whether pneumonia actually was the underlying CoD in all of these cases can be discussed. It is possible that in some of these cases, pneumonia was the immediate, but not the underlying CoD. Nevertheless, if it is the only disease reported in the death certificate, it would be registered as the underlying cause. As we noted in our discussion of cardiovascular diseases, whether this disease is listed as the underlying CoD depends on the level of knowledge the treating physicians have about the centenarian's health when they fill in the death certificate.

The group of other respiratory diseases that could be listed as the cause of death includes chronic obstructive pulmonary disease (COPD) and asthma. It is possible that a proportion of the deaths attributed to pneumonia may have actually been caused by an undiagnosed or unknown COPD.

8.6.3 Cancer

In our study, we found that the proportion of deaths in which cancer was listed as the underlying CoD was much lower among centenarians than among the 85–99-year-old group, and was even lower among the semi-supercentenarians (2.1%). Whether a death is caused by cancer depends of the severity of the cancer; i.e. the stage and the expansion of metastases. However, in the few existing autopsy studies on this age group, metastases were rarely observed in centenarians (Ishii and Sternby 1978c; Motta et al. 2010; Pavlidis et al. 2012). It is possible that other causes induced by the cancer – such as bleeding due to stomach cancer or pneumonia due to upper respiratory tract cancer – were reported as the main causes. In these cases, cancer may have been overlooked as the underlying CoD (Stanta et al. 1997).

8.6.4 Digestive, Urinary, and Endocrine Diseases

Although the shares of deaths attributable to these categories of disease are small (about 2% each), both the proportions of deaths from and the mortality rates for these three groups of CoDs more than doubled from the 1970s to the 2010–2012 period, when the mortality rate for each of these causes was higher than 10 per 1000 person-years. The endocrine disease group includes diabetes. This shift may have been the result of an increase in the numbers of older patients with diabetes who survived to very high ages. Moreover, an increase in the number of centenarians who were treating their arthritis by taking pain-relieving medicines such as NSAID, which may cause fatal gastro-intestinal bleeding (Wasteson et al. 2012), could explain the increase in the mortality rate for digestive diseases. In the few autopsy studies that included selected centenarian deaths, the proportion of deaths caused by urinary tract or genital diseases was found to be very low (less than 1%) among the nonagenarians and the centenarians in New Zealand, and to be zero among the centenarians who died at home in Austria (Berzlanovich et al. 2005).

8.6.5 *Mental Diseases*

This group of CoDs includes the ICD codes for dementia (F00-F03). The total proportion of deaths attributed to mental diseases is relatively low (about 4%), but the mortality rate for this group increased sixfold over the examined period. This shift reflects the increase in the number of older adults with dementia and the high prevalence of dementia among Danish centenarians – of about 50% (including mild dementia), according to the first study on Danish centenarians (Andersen-Ranberg et al. 2001b). However, this trend may also be partly due to the increased awareness and use of these diagnoses among physicians when completing the death certificate. Furthermore, it may have become more acceptable in recent years to report dementia as the underlying CoD instead of senility, fatigue, cachexia, or other ill-defined conditions/senility.

8.6.6 *Ill-Defined Conditions/Senility*

The group of ill-defined conditions/senility was probably listed as the underlying CoD when the physician who filled in the death certificate did not know the exact disease that caused the death. The proportion of registered deaths in which this CoD was listed increased dramatically over the study period, to more than one-quarter of the centenarian deaths and to more than one-third of the semi-supercentenarian deaths.

Evans et al. (2014) found that the proportion of deaths for which the CoD was listed as “old age” was high among centenarians in England (28.1%). This estimate is a little higher than our estimate for the share of deaths attributed to the group of “ill-defined conditions/senility” in the same period (24.2% in the 2000s). In Evans et al., the “old age” CoD group included the codes R53 (fatigue) and R54 (senility), while our CoD group of ill-defined conditions/senility included all R-codes (R0 to R99; i.e., including “lack of knowledge”). Although in our study the R54 code alone accounted for two-thirds of all the causes of deaths coded R0-R99, the share of deaths attributed to “old age” was found to be higher among English centenarians (28%) than among Danish centenarians in the most recent period. However, in both studies the proportion of deaths for which “old age” was listed as the CoD was very high; it was almost as high as the proportion of deaths from all three CVD groups in our study, and it was much higher than the proportion of deaths from all CVDs in Evans et al.

There are obviously some problems associated with using the ICD-10 codes of fatigue (R53), senility (R54), “lack of knowledge” (R99), and other R-codes. Among them are that physicians differ in their opinions about whether it is possible to die from old age. It can be argued that the physicians who reported one of these R-codes as the underlying CoD did so because they believe that ill-defined symptoms such as cachexia, fatigue, malaise, and senility are the result of degrading bodily functions and frailty. Like pneumonia, these symptoms might be seen as

resulting from very old age. Supporting this point of view is the marked increase in the proportion of deaths attributed to this group of ill-defined conditions/senility with increasing age among the Danish centenarians.

This increase may be related to the Danish Health Department's recommendation at the end of the twentieth century that physicians avoid the use of "causa ignota" (unknown cause) when completing death certificates. The increasing tendency to report ill-defined symptoms as the CoD may be attributable to the inability to make a clear diagnosis due to a lack of knowledge, and to the tendency to under-report certain diseases, such as cardiovascular diseases and cancer. According to John and Koelmeyer (2001), autopsies of nonagenarians and centenarians showed that they died of diseases, and not of "old age." But this conclusion was based on sudden deaths. It may be the case that a substantial proportion of the Danish centenarians (maybe about one-fifth), and especially of the semi-supercentenarians (maybe about one-fourth), died of "old age" – i.e., a combination of several diseases and organ deficiencies – and not due to one single cause.

8.6.7 Differences Between Age Groups and Gender

Some differences between the centenarians who died at ages 100–104 and those who died at ages 105+ were identified. The proportions of deaths from cardiovascular diseases and from cancer were a little lower among the semi-supercentenarians than among the 100–104-year-old centenarians; while the proportions of deaths from accidents (falls), other respiratory diseases (including COPD), and ill-defined conditions/senility were higher among the semi-supercentenarians. The use of the R54 code ("old age," senility) in particular was substantially higher.

The comparison of the underlying CoDs reported for the centenarians and for the 85–99-year-olds showed that the differences between these age groups were substantial. These findings seem to confirm that serious forms of cancer were rarely reported as the underlying CoD among the centenarians, and that pneumonia and "old age" were important underlying CoDs among the Danish centenarians.

Male and female centenarians were shown to display different mortality patterns. The mortality rate observed among men indicates that men were more likely than women to have died from somatic diseases, while women were more likely than men to have died from mental diseases or ill-defined conditions/senility. Some of these gender differences could be attributable to the higher age structure of the centenarian women relative to that of the centenarian men. This gap could also be due in part to a higher detection rate of somatic diseases among men, especially of CVD. But since these differences were not large, it appears that having a very high age matters more than gender.

8.6.8 *Strengths and Weaknesses of the Study*

The strength of this study lies in the inclusion of the total number of registered deaths among centenarians in Denmark during a long period of more than 40 years. We have thereby avoided the selection of centenarian deaths, which was the basis for most of the previous studies, as reported in the introduction. Only the study for England by Evans et al. (2014) took a similar approach. Although this study included four times the number of centenarian deaths, it covered a shorter time period. Another strength of our study is that we were able to directly compare the centenarians with the 85–99-year-olds, and the semi-supercentenarians with the 100–104-year-olds.

However, when considering the findings of this study, it is important to take into account some possible barriers to ascertaining the cause of death. The shift in codes between the ICD-8 and the ICD-10 has been taken into consideration in the DRCD's classification of the CoD into 49 categories (see Table 8.1). One of the most reliable ways of clearly establishing the CoD is by performing an autopsy. However, in Denmark autopsies are performed on a very small proportion of the centenarians who die (less than 1% in the latest periods). Furthermore, as most of the Danish centenarians in our study did not die in a hospital (only about one-tenth died in a hospital), the death certificate would have been filled in by a general practitioner (GP) in the majority of these cases. This may help to explain the tendency to report ill-defined conditions/senility as the underlying CoD. As recent recommendations discourage physicians from listing an unknown CoD (code R99), the use of the ill-defined conditions/senility CoD may have increased among GPs.

In sum, we think that our findings regarding the distribution and the development over time of underlying CoDs among Danish centenarians approximately capture the real situation. However, we also think that the increasing tendency to report senility ("old age") as the underlying CoD is partly due to the under-diagnosis of diseases among centenarians, especially of heart diseases; and is partly due to an actual increase in the number of people dying from a combination of multi-morbidity and organ deficiencies that can be accurately described as "old age." In most cases, the underlying CoD listed was mainly based on the knowledge of the GPs who filled out the death certificate. It can be difficult for GPs to disentangle which disease initiated the events leading to death.

References

- Andersen-Ranberg, K., Schroll, M., & Jeune, B. (2001a). Healthy centenarians do not exist, but autonomous centenarians do: A population-based study of morbidity among Danish centenarians. *Journal of the American Geriatrics Society*, 49(7), 900–908.
- Andersen-Ranberg, K., Vasegaard, L., & Jeune, B. (2001b). Dementia is not inevitable: A population study fo Danish Centenarians. *Journal of Gerontoogy. Series B: Psychological Sciences & Social Sciences*, 56B, 152–159.

- Andersen-Ranberg, K., Fjederholt, K. T., Madzak, A., Nybo, M., & Jeune, B. (2013). Cardiovascular diseases are largely underreported in Danish centenarians. *Age and Ageing*, 42(2), 249–253.
- Berzlanovich, A. M., Keil, W., Waldhoer, T., Sim, E., Fasching, P., & Fazeny-Dörner, B. (2005). Do centenarians die healthy? An autopsy study. *The Journals of Gerontology Series A, Biological Sciences and Medical Sciences*, 60(7), 862–865.
- Evans, C. J., Ho, Y., Daveson, B. A., Hall, S., Higginson, I. J., & Gao, W. (2014). Place and cause of death in centenarians: A population-based observational study in England, 2001 to 2010. *Public Library of Science Medicine Journal*, 11(6).
- Ishii, T., & Sternby, N. H. (1978a). Pathology of centenarians. I. The cardiovascular system and lungs. *Journal of the American Geriatrics Society*, 26(3), 108–115.
- Ishii, T., & Sternby, N. H. (1978b). Pathology of centenarians. II. Urogenital and digestive systems. *Journal of the American Geriatrics Society*, 26(9), 391–396.
- Ishii, T., & Sternby, N. H. (1978c). Pathology of centenarians. III. Osseous system, malignant lesions, and causes of death. *Journal of the American Geriatrics Society*, 26(12), 529–533.
- John, S. M., & Koelmeyer, T. D. (2001). The forensic pathology of nonagenarians and centenarians: Do they die of old age? (The Auckland experience). *The American Journal of Forensic Medicine and Pathology*, 22(2), 150–154.
- Louhija, J. (1995). *Finnish centenarians: A clinical epidemiological study*. Helsinki: Geriatric Unit, Second Department of Medicine, University of Helsinki.
- Motta, M., Bennati, E., Vacante, M., Stanta, G., Cardillo, E., Malaquarnera, M., & Giarelli, L. (2010). Autopsy reports in extreme longevity. *Archives of Gerontology and Geriatrics*, 50(1), 48–50.
- Pavlidis, N., Stanta, G., & Audisio, R. A. (2012). Cancer prevalence and mortality in centenarians: A systematic review. *Critical Reviews in Oncology/Hematology*, 83(1), 145–122.
- Stanta, G., Campagner, L., Cavallieri, F., & Giarelli, L. (1997). Cancer of the old. What we have learned from autopsy studies. *Clinics in Geriatric Medicine*, 13(1), 55–68.
- Sundhedsstyrelsen. (2002). *Dødsårsagsregisteret*. Copenhagen.
- Wasteson, J. W., Parker, M. G., Fastbom, J., Thorslund, M., & Johnell, K. (2012). Drug use in centenarians compared with nonagenarians and octogenarians in Sweden: A nationwide register-based study. *Age Ageing*, 41(2), 218–224.

Open Access This chapter is licensed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.