Original Contribution

Cause-specific Mortality of Grand Multiparous Women in Finland

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Knowledge is limited on mortality of grand multiparous women (≥5 deliveries), whose hormonal, metabolic, and social conditions differ from the average. The authors studied overall and cause-specific mortality in 1974–2001 among 87,922 grand multiparous women including 3,678 grand grand multiparous women (≥10 deliveries) in Finland. Standardized mortality ratios were defined as ratios of observed to expected numbers of deaths, both derived from national cause-of-death files. During follow-up, 18,870 grand multiparous women and 625 grand grand multiparous women died (standardized mortality ratios (SMRs) = 0.95 and 1.01, respectively). Decreased mortality among grand multiparous women was found for cancers of the breast (SMR = 0.64, 95% confidence interval (CI): 0.59, 0.69), corpus uteri (SMR = 0.68, 95% CI: 0.56, 0.80), ovary (SMR = 0.68, 95% CI: 0.60, 0.75), bladder (SMR = 0.59, 95% CI: 0.41, 0.82), and respiratory tract (SMR = 0.80, 95% CI: 0.72, 0.88). The only malignant tumor associated with elevated mortality was kidney cancer (SMR = 1.38, 95% CI: 1.21, 1.56). The standardized mortality ratio was also low for dementia (SMR = 0.78, 95% CI: 0.72, 0.84), respiratory diseases (SMR = 0.80, 95% CI: 0.75, 0.85), and accidents and violent causes (SMR = 0.79, 95% CI: 0.73, 0.84). Mortality from diabetes mellitus (SMR = 1.42, 95% CI: 1.29, 1.55) and ischemic heart disease (SMR = 1.10, 95% CI: 1.08, 1.13) was increased. According to this study, overall mortality among grand multiparous women is not elevated. Low mortality from cancers is offset by higher mortality from cardiovascular conditions and diabetes mellitus.

Abbreviations: CI, confidence interval; GM, grand multiparous; GGM, grand grand multiparous; SMR, standardized mortality ratio.

We previously reported a low incidence of cancers of the breast and corpus uteri and a slightly increased incidence of cervical cancer among grand multiparous (GM) women, compared with all women, in Finland (1–3). Pregnancies and sex-related hormones may induce significant changes in factors controlling malignant transformation of reproductive organs (4–7). They also predispose to diabetes, pre-eclampsia, hypertension, and obesity, which are well-known risk factors for mortality (8–16). Little is known about the cumulative effects of numerous childbearings on long-term mortality (15, 17–22). We therefore examined the overall and cause-specific mortality among all GM women in Finland during the period 1974–2001.

MATERIALS AND METHODS

A study cohort of all women in Finland with at least five deliveries (N = 87,922; the whole GM cohort) and of those 3,678 women with at least 10 deliveries (grand grand
multiparous (GGM) women) from January 1, 1974, to December 31, 1997, was drawn from the national population register (stillborn babies were not taken into account). Records were linked with the national cause-of-death files of Statistics Finland by using a unique personal identification code up to the year 2001. Deaths had been classified according to the International Classification of Diseases (the Eighth Revision in 1969–1986, the Ninth Revision in 1987–1995, and the Tenth Revision in 1996–2001). Person-years were calculated from the fifth or 10th birth or January 1, 1974, whichever was later, until death or December 31, 2001, by 5-year age groups. Standardized mortality ratios were defined as ratios of observed to expected numbers of deaths by using cause-specific mortality among all Finnish women as a reference. The confidence intervals for the standardized mortality ratios were based on the Poisson distribution.

RESULTS

Among the 87,922 GM women, 18,870 deaths occurred, slightly fewer than expected (n = 19,819) from the whole female population (standardized mortality ratio (SMR) = 0.95, 95 percent confidence interval (CI): 0.94, 0.95). For the GGM women, the standardized mortality ratio did not deviate from the national average (625 deaths; expected deaths, 621; SMR = 1.01, 95 percent CI: 0.93, 1.08).

Among the GM women, overall cancer mortality was 11 percent lower than expected (table 1). It was significantly low for cancers of the breast (36 percent deficit), corpus uteri (32 percent), ovary (32 percent), bladder (41 percent), and respiratory organs (20 percent). Significantly high mortality was found for cancer of the kidney (38 percent excess). The standardized mortality ratio for cervical cancer did not differ from the average.

The standardized mortality ratios for cardiovascular diseases, notably ischemic heart disease and cerebrovascular diseases, slightly exceeded the national average (table 2). The standardized mortality ratio for diabetes mellitus was increased by 42 percent.

Mortality from diseases of the respiratory organs was 20 percent lower than expected (table 2). Mortality from tuberculosis was decreased by 40 percent and from diseases of the bladder and from genitourinary diseases by 15 percent. The standardized mortality ratios for dementia and Alzheimer’s disease, as well as for other diseases of the nervous system and sense organs, were significantly low (22–23 percent deficit) (table 2).

Among GM women, mortality from accidents was lower than average (21 percent deficit). The standardized mortality ratio was especially low for accidental poisoning (43 percent) and suicides (43 percent) (table 3). Only traffic accidents were associated with high mortality (17 percent excess).

Among the GGM women, the standardized mortality ratios were 0.70 (95 percent CI: 0.45, 1.03; 24 deaths) for breast cancer, 0.43 (95 percent CI: 0.16, 0.94; six deaths) for ovarian cancer, and 0.34 (95 percent CI: 0.04, 1.22; two deaths) for corpus uterine cancer. The standardized

<table>
<thead>
<tr>
<th>Table 1. Standardized mortality ratios for cancer, by site, in grand multiparous women* in Finland, 1974–2001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause of death, by site (ICD-10† code(s))</strong></td>
</tr>
<tr>
<td>All neoplasms (C00–C97)</td>
</tr>
<tr>
<td>Breast (C50)</td>
</tr>
<tr>
<td>Cervix uteri (C53)</td>
</tr>
<tr>
<td>Corpus uteri (C54–C55)</td>
</tr>
<tr>
<td>Ovary (C56)</td>
</tr>
<tr>
<td>Lip, oral cavity, and pharynx (C00–C14)</td>
</tr>
<tr>
<td>Esophagus (C15)</td>
</tr>
<tr>
<td>Stomach (C16)</td>
</tr>
<tr>
<td>Colon (C18, 19)</td>
</tr>
<tr>
<td>Rectum, anus, and anal canal (C20–21)</td>
</tr>
<tr>
<td>Liver and intrahepatic bile ducts (C22)</td>
</tr>
<tr>
<td>Pancreas (C25)</td>
</tr>
<tr>
<td>Larynx, trachea, bronchus, and lung (C32–C34)</td>
</tr>
<tr>
<td>Malignant melanoma of the skin (C43)</td>
</tr>
<tr>
<td>Kidney (C64)</td>
</tr>
<tr>
<td>Bladder (C67)</td>
</tr>
<tr>
<td>Lymphoid, hematopoietic, and related tissue (C81–C96)</td>
</tr>
</tbody>
</table>

* Defined as women having ≥5 deliveries.
† ICD-10, International Classification of Diseases, Tenth Revision; SMR, standardized mortality ratio; CI, confidence interval.
mortality ratios were 1.28 (95 percent CI: 1.11, 1.47; 192 deaths) for ischemic heart disease and 1.18 (95 percent CI: 0.94, 1.45; 86 deaths) for cerebrovascular diseases. The standardized mortality ratio for diabetes mellitus was 1.81 (95 percent CI: 1.06, 2.90; 17 deaths). Decreased mortality was seen for suicides (SMR = 0.26, 95 percent CI: 0.05, 0.76; three deaths) and dementia and Alzheimer’s disease (SMR = 0.78, 95 percent CI: 0.45, 1.24; 17 deaths).

**DISCUSSION**

This study reports the overall and cause-specific standardized mortality ratios for GM women in a national cohort from a country with well-organized health care systems and with registers that include reliable data on births and deaths. According to our study, overall mortality among GM women was slightly lower than average. This finding is in line with a Norwegian study (20) but disagrees with studies from England and Wales (17, 18, 22). For the GGM women, the overall standardized mortality ratio was average. The low mortality among GM women in our study was mainly due to low rates of cancers of the breast, ovary, corpus uteri, and lung and, to a lesser extent, to low mortality for dementia and Alzheimer’s disease, respiratory diseases, and most kinds of violent causes. Increased mortality was found for cancer of the kidney; all metabolic diseases, mainly diabetes mellitus; and diseases of the circulatory organs. The figures for the latter two were especially high in GGM women.

The Finnish population of GM women represents 2.6 percent of all parturients during the study period in the north and 0.5 percent in the south (23). Longevity of women is poorer in the north of Finland than elsewhere (24) mainly because of 20–30 percent higher mortality from ischemic heart disease (25). This conforms to our finding of increased cardiovascular deaths in GM women, the majority of whom are from northern Finland.

Most GM women belong to the Laestadian movement within the Lutheran church. All kinds of contraception are forbidden; otherwise, however, the living habits of Laestadians do not differ markedly from those of other Finns. Smoking is permitted, but alcohol consumption is rare. The percentage of smokers (7 percent) among Finnish GM

**TABLE 2. Standardized mortality ratios for diseases other than cancer in grand multiparous women* in Finland, 1974–2001**

<table>
<thead>
<tr>
<th>Cause of death (ICD-10† code(s))</th>
<th>Observed (no.)</th>
<th>Expected (no.)</th>
<th>SMR†</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious and parasitic diseases (A00–B99, J65)</td>
<td>150</td>
<td>183</td>
<td>0.82</td>
<td>0.69, 0.95</td>
</tr>
<tr>
<td>Tuberculosis (A15–A19, B90, J65)</td>
<td>49</td>
<td>81</td>
<td>0.60</td>
<td>0.45, 0.79</td>
</tr>
<tr>
<td>Endocrine, nutritional, and metabolic diseases (E00–E90)</td>
<td>455</td>
<td>338</td>
<td>1.35</td>
<td>1.22, 1.47</td>
</tr>
<tr>
<td>Diabetes mellitus (E10–E14)</td>
<td>424</td>
<td>299</td>
<td>1.42</td>
<td>1.29, 1.55</td>
</tr>
<tr>
<td>Other endocrine, nutritional, and metabolic diseases (E00–E07, E15–E90)</td>
<td>31</td>
<td>39</td>
<td>0.79</td>
<td>0.53, 1.11</td>
</tr>
<tr>
<td>Dementia and Alzheimer’s disease (F01, F03, G30, R54)</td>
<td>631</td>
<td>804</td>
<td>0.78</td>
<td>0.72, 0.84</td>
</tr>
<tr>
<td>Other diseases of the nervous system and sense organs (G00–G29, G31.0–G311, G31.8–G620, G622–G720, G722–H95)</td>
<td>282</td>
<td>366</td>
<td>0.77</td>
<td>0.68, 0.86</td>
</tr>
<tr>
<td>Diseases of the circulatory system (I00–I25, I27–I99)</td>
<td>9,376</td>
<td>8,885</td>
<td>1.06</td>
<td>1.03, 1.07</td>
</tr>
<tr>
<td>Ischemic heart diseases (I20–I25)</td>
<td>5,494</td>
<td>4,976</td>
<td>1.10</td>
<td>1.08, 1.13</td>
</tr>
<tr>
<td>Other heart diseases (I30–I425, I427–I52), excluding rheumatic heart diseases</td>
<td>665</td>
<td>728</td>
<td>0.91</td>
<td>0.84, 0.98</td>
</tr>
<tr>
<td>Cerebrovascular diseases (I60–I69)</td>
<td>2,477</td>
<td>2,415</td>
<td>1.03</td>
<td>0.99, 1.06</td>
</tr>
<tr>
<td>Diseases of the respiratory system (J00–J64, J66–J99)</td>
<td>851</td>
<td>1,060</td>
<td>0.80</td>
<td>0.75, 0.85</td>
</tr>
<tr>
<td>Influenza (J10–J11)</td>
<td>26</td>
<td>33</td>
<td>0.78</td>
<td>0.51, 1.14</td>
</tr>
<tr>
<td>Asthma (J45–J46)</td>
<td>72</td>
<td>86</td>
<td>0.84</td>
<td>0.66, 1.05</td>
</tr>
<tr>
<td>Pneumonia (J12–J18, J849)</td>
<td>469</td>
<td>612</td>
<td>0.77</td>
<td>0.70, 0.83</td>
</tr>
<tr>
<td>Bronchitis and emphysema (J40–J44, J47)</td>
<td>180</td>
<td>236</td>
<td>0.76</td>
<td>0.66, 0.87</td>
</tr>
<tr>
<td>Diseases of the digestive system (nonalcohol) (K00–K291, K293–K67, K71–K85, K861–K93)</td>
<td>554</td>
<td>584</td>
<td>0.95</td>
<td>0.87, 1.02</td>
</tr>
<tr>
<td>Diseases of the genitourinary system (N00–N99)</td>
<td>195</td>
<td>230</td>
<td>0.85</td>
<td>0.73, 0.96</td>
</tr>
<tr>
<td>Alcohol-related diseases and accidental poisoning by alcohol (F10, G312, G4051, G621, G721, I426, K292, K70, K960, K860, O354, P043, X45)</td>
<td>144</td>
<td>210</td>
<td>0.69</td>
<td>0.58, 0.80</td>
</tr>
</tbody>
</table>

* Defined as women having ≥5 deliveries.
† ICD-10, International Classification of Diseases, Tenth Revision; SMR, standardized mortality ratio; CI, confidence interval.
women during pregnancy is half that among all pregnant women (14 percent). Of GM women, about 50 percent were economically active in the 1990s and about 80 percent of them were entrepreneurs (mainly independent farmers) or white-collar workers. The respective proportions in the general female population were 75 percent and 65 percent. The GM women are nearly always married; during the mid-1990s, about 95 percent of the GM women were married, but, for all other parturients, the percentage was 67. The income of Finnish GM families may be satisfactory because of the allowance paid by the state for each child (23). Roos et al. (26) from Finland and Sweden demonstrated that married mothers who are employed had the best perceived health in both countries, whereas income status had only a small effect on that patterning. The net effects of those factors on mortality are difficult to determine. In addition, the primary health status of GM women is probably better than that of average Finnish women.

Perinatal mortality among Finnish GGM women was low in each birth category (1.1 percent for first-born and 1.6 percent for 10th- to 20th-born children). The frequency of large-for-gestational-age children increased respectively from 7.4 percent to 22.4 percent. The frequency of gestational diabetes and hypertensive disease increased with advancing number of deliveries (11). Such changes increase the risk of contracting diabetes (27, 28) or hypertensive and cardiovascular diseases (15, 29, 30) in older age.

Reliability regarding the causes of death listed in the national cause-of-death files was deemed adequate for our purposes. The agreement of diagnoses of myocardial infarction and stroke in the national death files with those in a large prospective study was reasonable (31), and a review of cardiovascular diagnoses on the death certificates confirmed 85 percent of them in autopsy (32). A recent comparison of death-certificate diagnoses of stroke with diagnoses made in an independent study found agreement in more than 90 percent of the instances (33). For cancer deaths, comparability of the official mortality statistics with cancer registry information, known to be very accurate, was already high in the 1970s (34). Although no validity studies pertaining to other diagnostic classifications are known to be available in this country, potential misclassification would be unlikely to introduce a bias regarding comparisons between multiparous and other women.

Of the decreased overall cancer mortality in our study (11 percent deficit; about 600 cases in absolute terms), 90 percent was attributable to breast, corpus uteri, and ovarian cancers. The specific hormonal milieu during pregnancy, repeated several times in GM women, may counteract malignant transformation in most gynecologic organs, with cervical cancer as the only exception (1, 4–6, 35). The standardized mortality ratio for all cancer mortality (SMR = 0.89) in our study was actually lower than that observed in Norwegian (SMR = 0.97) (20) and English (SMR = 0.97) (18) studies. There might be differences in lifestyle and social support of life between those countries. For example, smoking in general and especially by pregnant women is more common in Norway than in Finland (20, 36).

The standardized mortality ratios for breast cancer (SMR = 0.64) and corpus uteri cancer (SMR = 0.68) were somewhat higher than the respective standardized incidence ratios of 0.55 (95 percent CI: 0.52, 0.57) and 0.57 (95 percent CI: 0.52, 0.63) in our previous studies (1, 2). An explanation for this discrepancy regarding breast cancer may be a delayed diagnosis in GM women. The standardized mortality ratio for breast cancer in the present study (SMR = 0.64) was about the same as the standardized incidence ratios for advanced breast cancer in the earlier study; the standardized incidence ratio for breast cancer with regional metastases was 0.63 and for distant metastases was 0.66 (1). For corpus uteri cancer, the standardized incidence ratios did not vary by stage. The standardized mortality ratio (SMR = 1.10) for cervical cancer did not essentially differ from the respective standardized incidence ratio of 1.13 (95 percent CI: 0.98, 1.29) (3). It should be borne in mind that, in terms of cancer, incidence is more a reliable measure of disease occurrence and often gives different risk patterns than mortality does (37). The main reason is varying survival in population subgroups (38) and, sometimes, factors related to the choice of underlying cause of death when several causes are mentioned on the death certificate.

In our sample, mortality from cancer of the bladder was low, as was also found in previous studies (39, 40). Our investigation favors the hypothesis that oncogens in transitional

### TABLE 3. Standardized mortality ratios for violent causes for grand multiparous women* in Finland, 1974–2001

<table>
<thead>
<tr>
<th>Cause of death (ICD-10†)</th>
<th>Observed (no.)</th>
<th>Expected (no.)</th>
<th>SMR†</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All accidents and violent causes</td>
<td>783</td>
<td>995</td>
<td>0.79</td>
<td>0.73, 0.84</td>
</tr>
<tr>
<td>Accidental falls</td>
<td>199</td>
<td>248</td>
<td>0.80</td>
<td>0.69, 0.91</td>
</tr>
<tr>
<td>Land traffic accidents</td>
<td>211</td>
<td>181</td>
<td>1.17</td>
<td>1.02, 1.33</td>
</tr>
<tr>
<td>Accidental poisoning other than alcohol</td>
<td>33</td>
<td>58</td>
<td>0.57</td>
<td>0.39, 0.79</td>
</tr>
<tr>
<td>Drowning</td>
<td>21</td>
<td>22</td>
<td>0.96</td>
<td>0.59, 1.46</td>
</tr>
<tr>
<td>Suicides and sequelae of intentional self-harm</td>
<td>173</td>
<td>306</td>
<td>0.57</td>
<td>0.48, 0.65</td>
</tr>
<tr>
<td>Assault and sequelae of assaults</td>
<td>40</td>
<td>34</td>
<td>1.18</td>
<td>0.84, 1.60</td>
</tr>
</tbody>
</table>

* Defined as women having ≥5 deliveries.
† ICD-10, International Classification of Diseases, Tenth Revision; SMR, standardized mortality ratio; CI, confidence interval.
cell tissue of the human bladder are influenced by sex hormones, and that the hormonal changes related to pregnancy thereby reduce the risk (39). The standardized mortality ratio \( \text{SMR} = 0.59 \) appears to be too low to be explained by infrequent smoking alone, which is the most powerful, single factor in the etiology of bladder cancer (40).

Lung cancer was associated with a standardized mortality ratio of 0.80. The standardized mortality ratio for all other respiratory diseases was also 0.80. As explained above, pregnant women in Finland smoke less than nonpregnant women, and GGM women with a short interpregnancy interval (8.9 (standard deviation, 5.6) months) smoke less than women with fewer children (10). Our results differ from those observed by Kvale et al. (20), who noted increased mortality from all respiratory conditions—including asthma, pneumonia, bronchitis, and emphysema—and from lung cancer (standardized incidence ratio \( R = 1.4 \)) among GM women, which they attributed to the higher prevalence of smoking among Norwegian women than Finnish women (36). Our results support the hypothesis that estrogen and other steroid hormones in lung tissue may reduce the risk of lung cancer, as observed among the users of oral contraceptives or hormone replacement therapy (41–43).

The standardized mortality ratio for cancer of the colon was also slightly lowered. This finding was expected because the colonic epithelium is dependent on ovarian hormones (44–46).

Mortality from cancer of the kidney was 38 percent higher than the national average, which is in line with the 40 percent higher mortality from this cancer seen among Swedish GM women compared with nulliparous women (47). Some other studies did not show any association between risk of kidney cancer and number of pregnancies (18, 48), Chow et al. (49, 50) and Lindblad et al. (51) speculated that hormonal factors per se are important in the pathogenesis of this malignancy, and that obesity associated with childbearing may lead to a permanent hyperestrogenic environment and increased levels of insulin and insulin-like growth factors. These hormonal factors with hypertension during and after pregnancies might influence factors involved in renal carcinogenesis. Obesity (body mass index \( >30 \) kg/m\(^2\)) has been found to increase the risk of kidney cancer (52).

As expected from previous works (17, 18, 20, 53), our study found a slightly increased risk of death from ischemic heart disease, cerebrovascular diseases, and diabetes mellitus. Pregnancy often induces diabetogenic and hypertensive changes, the likelihood of which increases with the number of pregnancies (9, 11, 15, 54, 55). Indeed, mortality from these diseases was markedly higher in GGM than in GM women. Repeated pregnancies increase the risk of hypertensive disorders and gestational diabetes, as shown by a Finnish study on GGM women, and they also cause a gradual and persistent increase in body weight (11). In all Finnish women, the prevalence of overweight increased gradually with the number of children (56). An average increase of 3.3 kg/m\(^2\) in body mass index between the first and sixth pregnancies was reported in Sweden (47). Parity has been found to explain the presence of obesity and greater central accumulation of body fat, a low concentration of high density lipoprotein cholesterol, and insulin resistance in women older than age 55 years (9, 56–59). The biologic effects of pregnancy may thus increase morbidity and mortality associated with several diseases years after the reproductive age ends (29).

Few studies have focused on number of children and the risk of dementia and Alzheimer’s disease (61, 62). To our knowledge, the present finding of a markedly lowered risk of death from these conditions is new. In previous results, parous women, compared with nulliparous women, have had a higher risk of Alzheimer’s disease (61–63). The role of ovarian hormones in neuroprotection has remained unclear despite intensive research (64, 65). Mothers who have many children live an active life, which might protect the brain and the nervous system from early degeneration. Having a large number of children is said to prevent suicides due to maternity (66, 67), not marriage per se (68). The 40 percent and 74 percent lower-than-expected risk of suicide for GM and GGM women, respectively, is in line with this hypothesis.

Heavy alcohol consumption during pregnancy is uncommon in Finland. It is likely to be most rare in the Finnish GM population, many of whom have a special religious persuasion. This finding could explain the low standardized mortality ratio \( \text{SMR} = 0.69 \) for alcohol-related diseases and accidents.

Deaths from traffic accidents were common among the GM women. Many GM families live in the sparsely populated area of northern Finland, where distances are long and the families are therefore predisposed to traffic accidents.

In conclusion, Finnish GM women had slightly lower-than-average mortality (949 deaths fewer than expected), mainly from cancers (gynecologic and others), although this lower rate was partly outweighed by relatively high mortality from cardiovascular diseases and diabetes mellitus. Among women with at least 10 deliveries, overall mortality was totally offset by high mortality from the latter two causes. Suggested factors underlying the findings would be preventive effects of hormones on the development of cancers, and harmful effects of overweight on the pancreas and cardiovascular system. However, in the absence of individual data on possible confounders, the independent effect of parity remains open.

ACKNOWLEDGMENTS

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REFERENCES


