



Cohort Profile

Cohort Profile: The Swedish Women's Lifestyle and Health cohort

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Why was the cohort set up?

In the early 1980s, a case-control study carried out in the USA found a strong association between oral contraceptive use and breast cancer risk among young women (<37 years at diagnosis), inducing fear of the public health consequences of oral contraceptives.¹ These findings needed to be reproduced in other populations; thus a Swedish/Norwegian research group set up a nationwide case-control study of oral contraceptive use and breast cancer in young women, which confirmed the elevated risk.² However, the results of these studies were debated, and several sources of bias in the case-control design were pointed out.^{3–5} Based on this criticism, it was decided to set up a large cohort study which would eliminate biases that may occur in the case-control design.

This led to the initiation of the Swedish Women's Lifestyle and Health (WLH) cohort in 1991. The study is carried out in strict coordination with a similar study in Norway—the Norwegian Women and Cancer Study (NOWAC) which includes approximately 60 000 young women. A cohort profile of this study has previously been published.⁶

The purpose of the WLH study was to create a large prospective cohort designed specifically to investigate the association between lifestyle factors (specifically exogenous hormones and dietary habits) and cancer and

cardiovascular disease in young women. Other outcomes have also been investigated, including overall mortality and psychiatric conditions.

The WLH study was co-funded by the Swedish Medical Products Agency, the Swedish Cancer Society and three pharmaceutical companies. The ongoing analyses and the follow-up questionnaire were funded by the Swedish Cancer Society and the Swedish Research Council.

Who is in the cohort?

Between 1991 and 1992, women were invited to participate in the WLH study. Inclusion criteria were age between 29 and 49 years (born between 1943 and 1962) and residence in the Uppsala Health Care Region, which comprises approximately one-sixth of the Swedish population. Altogether, 96 000 women were randomly selected from the Swedish Population Registry at Statistics Sweden based on their unique, 10-digit national registration number, which includes information on both date of birth and sex.⁷ The responsible data monitoring board and the ethical committee in Sweden approved the study design, and all women gave informed consent to participate in the study. The women were mailed an invitation to the study, along with the baseline questionnaire, which included a food

Table 1. Baseline characteristics of participants in the Women's Lifestyle and Health cohort, entire cohort and according to follow-up status. Median and 10–90 percentiles, unless otherwise stated

| | Baseline cohort N = 49 259 | Responders to the follow-up questionnaire N = 34 402 | Non-responders to the follow-up questionnaire N = 14 857 |
|-------------------------------|-------------------------------|--|--|
| Age at enrolment, years | 40 (32–48) | 40 (32–48) | 40 (32–48) |
| BMI, kg/m ² | 23 (20–28) | 22.5 (20–28) | 23 (20–28.5) |
| Missing, N (%) | 2024 (4.11%) | 1213 (3.53%) | 811 (5.46%) |
| Smoking status, N (%) | | | |
| Never | 20 476 (41.57%) | 14 682 (42.68%) | 5794 (39.00%) |
| Former | 18 287 (37.12%) | 12 821 (37.27%) | 5466 (36.79%) |
| Current | 10 496 (21.31%) | 6899 (20.05%) | 3597 (24.21%) |
| Education, N (%) | | | |
| 0–10 years | 14 491 (30.08%) | 9160 (27.16%) | 5331 (35.88%) |
| 11–13 years | 18 797 (39.02%) | 13 334 (39.53%) | 5463 (36.77%) |
| >13 years | 14 880 (30.89%) | 11 236 (33.31%) | 3644 (24.53%) |
| Missing | 1091 (2.21%) | 672 (1.95%) | 419 (2.82%) |
| Postmenopausal status, N (%) | | | |
| Premenopausal | 43 112 (87.52%) | 30 372 (88.29%) | 12 740 (85.75%) |
| Postmenopausal | 4612 (9.37%) | 3091 (8.98%) | 1523 (10.25%) |
| Missing | 1533 (3.11%) | 939 (2.73%) | 594 (4.00%) |
| Oral contraceptive use, N (%) | | | |
| Never | 8089 (16.42%) | 5439 (15.81%) | 2650 (17.84%) |
| Former | 34 529 (70.10%) | 24 355 (70.80%) | 10 174 (68.48%) |
| Current | 6246 (12.68%) | 4402 (12.80%) | 1844 (12.41%) |
| Missing | 395 (0.80%) | 206 (0.60%) | 189 (1.27%) |
| Parity, N children | 2 (0–3) | 2 (0–3) | 2 (0–3) |
| Missing, N (%) | 7044 (14.30%) | 4676 (13.59%) | 2368 (15.94%) |
| Physical activity, N (%) | | | |
| 1 (very low) | 2079 (4.22%) | 1250 (3.63%) | 829 (5.58%) |
| 2 (low) | 4992 (10.13%) | 3544 (10.30%) | 1448 (9.75%) |
| 3 (moderate) | 28 007 (56.86%) | 19 320 (56.16%) | 8687 (58.47%) |
| 4 (high) | 7895 (16.03%) | 5874 (17.07%) | 2021 (13.60%) |
| 5 (very high) | 3950 (8.02%) | 2940 (8.55%) | 1010 (6.8%) |
| Missing | 2336 (4.74%) | 1474 (4.28%) | 862 (5.80%) |
| Total energy intake, KJ/day | 6371.649 (4108.83–9156.69) | 6420.867 (4211.52–9159.79) | 6245.77 (3863.3–9147.12) |
| Missing, N (%) | 125 (0.25%) | 49 (0.14%) | 76 (0.51%) |
| Alcohol intake, g/day | 2.27 (0–8.38) | 2.41 (0–8.48) | 1.97 (0–8.07) |
| Missing, N (%) | 6348 (12.89%) | 4043 (11.75%) | 2305 (15.51%) |

frequency questionnaire. In total, 49 259 women (51%) completed and returned the baseline questionnaire, and were thus included in the final cohort.

The baseline characteristics of the participants are shown in Table 1. The median age at enrolment was 40 years, meaning that most women were premenopausal at the time of enrolment. The cohort is generally well-educated, with 68% having completed more than 10 years of schooling, and they also led a generally healthy lifestyle. The median BMI at baseline was 23, only 21% were smokers and only 4% fell into the lowest category of physical activity. Alcohol intake in the cohort was also quite low at baseline, with a median intake of 2.27 g/day. Finally, 13% of the women used oral contraceptives.

How often have they been followed up?

The participants in the WLH cohort completed a baseline questionnaire in 1991–92. A follow-up questionnaire was sent in 2003 to all women still alive and residing in Sweden at that time. The response rate for the follow-up questionnaire was 73% (Figure 1).

The baseline characteristics of the entire cohort, as well as of responders and non-responders to the follow-up questionnaire, are presented in Table 1. A selection of healthy individuals into cohort studies is often reported, but in the WLH study it seems that this healthy volunteer bias persisted in the follow-up cohort. Indeed, non-responders were more likely to smoke at baseline, to have a shorter education and to be less physically active. In contrast, they

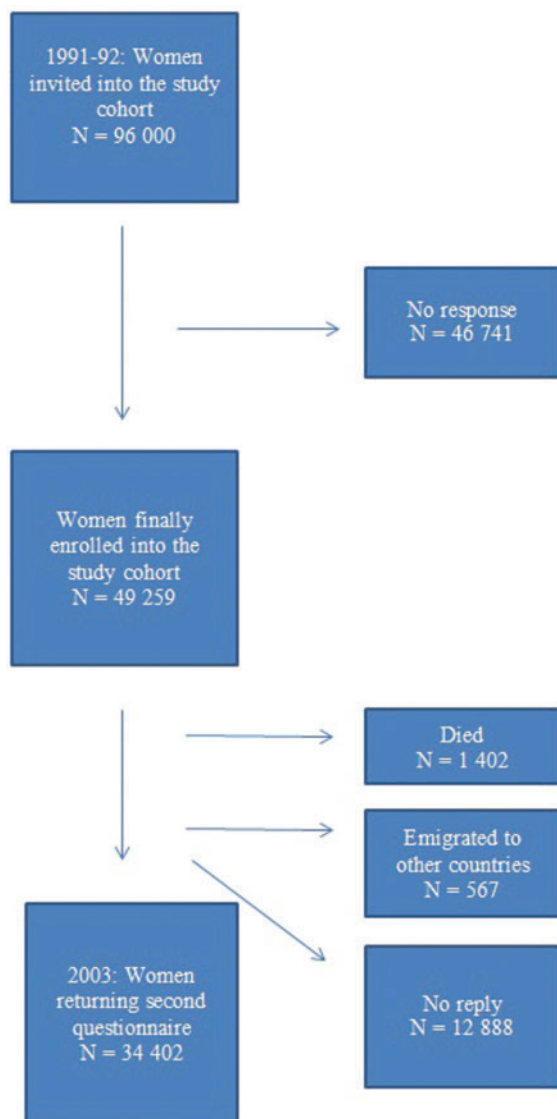


Figure 1. Flowchart of participants invited and finally included in the WLH-study.

generally reported a lower alcohol intake at baseline. Non-responders to the follow-up questionnaire were also more likely to have missing information on demographics and lifestyle in the baseline questionnaire. However, it should be noted that the difference between responders and non-responders at follow-up might be partly explained by the fact that non-responders included those who had died between baseline and follow-up, which may introduce some degree of bias towards an unhealthy lifestyle.

Beside the questionnaires, all participants are continuously monitored through linkage to Swedish registries on death, inpatient care and emigration. This is made possible through the unique Swedish national registration number, which is assigned to all Swedish citizens and allows linkage between registries and between cohort data and registries.

At present, no new follow-up questionnaire is planned, but the women are continuously followed up through linkage to registries.

What has been measured?

Questionnaire data

Baseline questionnaires were mailed in two rounds: one in 1991 and one in 1992. The baseline questionnaire included a detailed assessment of hormonal and reproductive factors, including menstrual history, use of hormone replacement therapy, pregnancies and breastfeeding, oral contraceptive use, disease history (both the woman's own history and family history of diseases), anthropometric measures, occupational history, emotional support, lifestyle factors (e.g. smoking and physical activity), skin and hair colour, sun/ultraviolet light exposure and sensitivity and an 80-item food frequency questionnaire. To facilitate recall of oral contraceptive use, a colour brochure with pictures of almost all contraceptive pill packages ever sold in Sweden was included.

In 2003, all participants still living in Sweden were sent a second questionnaire to update the assessment of lifestyle habits. Furthermore, we added questions on topics that had not been assessed in the baseline questionnaire, such as attitudes and feelings, sleeping habits and infertility treatment. A comparison of the topics covered in the baseline and follow-up questionnaires can be found in Table 2. Participants could complete the follow-up questionnaire on paper and return it by mail, or they could complete it as a web-based questionnaire, but the contents of the two questionnaires were the same.

The baseline and follow-up questionnaires are available in an English translation on the study webpage [http://www.meb.ki.se/~eliwei_2011/wlh/wlh_documents/] and from the principal investigator, upon request.

Registry data

Virtually complete follow-up has been achieved through linkage to a broad range of national, well-validated registries. Statistics Sweden collects the date of death or emigration for all Swedes.⁸ The Cause of Death Registry contains information on the underlying and contributory causes of death, recorded using International Classification of Diseases (ICD) codes, for all Swedes from 1961 onwards.⁹

The vital status of WLH participants is described in Table 3. The Swedish Cancer Registry contains information on all cancers diagnosed in Sweden since 1958, including cancer type (by ICD code), date of diagnosis, histology,

Table 2. Variables included in the baseline and follow-up questionnaire in the WLH cohort

| Topic | Baseline questionnaire | Follow-up questionnaire |
|---|------------------------|-------------------------|
| Country of origin | X | |
| Education | X | X |
| Mother's age at birth | X | |
| Siblings | X | |
| Menstrual history | X | X |
| Menopausal status | X | X |
| Use of hormone replacement therapy | X | X |
| Pregnancies, deliveries and breastfeeding | X | X |
| Infertility | | X |
| Oral contraceptive use | X | X |
| Other contraceptive use | X | X |
| Disease history | X | X |
| Self-assessed health status | X | |
| Anthropometric measures | X | X |
| Weight change during adult life | | X |
| Smoking habits | X | X |
| Physical activity | X | X |
| Personal description, i.e. colour of skin, hair and eyes | X | |
| Birthmarks | X | X |
| Sun habits, including use of sun lotion, solarium, beach holidays, sunburn, by decade | X | X |
| Food frequency questionnaire | X | |
| Alcohol use | X | X |
| Occupational environment | X | X |
| Private life | X | |
| Health examinations and health care | | X |
| Sleep | | X |
| Attitudes and feelings | | X |

pathology, morphology and the coding of tumour.¹⁰ The Swedish Cancer Registry has been validated, showing a high level of completeness.¹¹ The Swedish Inpatient Registry is a discharge registry; it contains information on all inpatient procedures that require hospital admission, including the main and up to eight secondary diagnoses, and date of discharge. It has nationwide coverage from 1987 onwards.¹² From 2001, the register also contains data on outpatient visits, including day surgery, as well as psychiatry from private and public providers.¹² The validity of the National Patient Registry is generally regarded as high, with a positive predictive value of 85–95% for different diagnoses.¹³ Since 2005, a Swedish Prescribed Drug Registry, containing data on all prescribed drugs administered in Sweden,¹⁴ has also been available for linkage and has allowed pharmacoepidemiological studies to be carried

Table 3. Vital status of participants included in the cohort as of 31 December 2012

| Vital status | N (% of original cohort) |
|---|--------------------------|
| Alive | 46 790 |
| Dead | 2470 |
| Main cause of death: cancer | 134 |
| Main cause of death: cardiovascular disease | 28 |
| Main cause of death: injuries/suicide | 60 |
| Main cause of death: other | 2248 |
| Emigrated | 1890 |

out. The incidence of cancer and cardiovascular disease outcomes in the cohort up to 31 December 2012 are presented in Table 4. Breast cancer, cardiovascular disease in general and the subgroups ischaemic heart disease, hypertensive disease and stroke, have the strongest power for scientific investigation. This is reflected in the studies already published from the WLH cohort, where these are the primary outcomes investigated.

What has it found? Key messages and publications

More than 50 peer-reviewed scientific papers have been published based on data from the WLH cohort alone, or in combination with data from other cohorts, such as the Norwegian sister-cohort NOWAC, or as part of larger meta-analyses. A complete and continuously updated list of publications emanating from the WLH study can be found on the study webpage [<http://ki.se/en/meb/womens-lifestyle-and-health>]. In this section we will summarize the findings related to the primary exposures the WLH study was designed to investigate.

Oral contraceptives

One of the primary exposures investigated in the WLH cohort is oral contraceptive use, which led to the initiation of the study in the first place. A large prospective study was published in 2002, including data from both Swedish and Norwegian women, which confirmed the findings of the original case-control study, i.e. an increased breast cancer risk following oral contraceptive use.¹⁵ Oral contraceptive use has also been examined in the WLH cohort in relation to ovarian cancer,¹⁶ myocardial infarction¹⁷ and stroke.¹⁸ The results showed a significantly lower risk of ovarian tumours among ever users of oral contraceptives, with a trend across duration of use,¹⁶ but no association was

Table 4. Incidence of cancer and cardiovascular disease (main diagnosis only) recorded in the cohort up to 31 December 2012; only most common diseases (>100 cases) included

| Disease | N (% of original cohort) |
|---|--------------------------|
| Cancers | |
| Breast cancer | 1849 (3.8) |
| Malignant melanoma of skin | 282 (0.6) |
| Bronchus and trachea, and lung specified as primary | 258 (0.5) |
| Corpus uteri | 222 (0.5) |
| Ovary, fallopian tube and broad ligament | 213 (0.4) |
| Brain and other parts of nervous system | 191 (0.4) |
| Large intestine, except rectum | 188 (0.4) |
| Rectum | 122 (0.3) |
| Other and unspecified sites | 113 (0.2) |
| Other endocrine glands | 108 (0.2) |
| Cardiovascular disease | |
| All cardiovascular disease | 8364 (17.0) |
| Diseases of veins, lymphatic vessels and lymph nodes | 3349 (6.8) |
| Other forms of heart diseases | 1542 (3.1) |
| Ischaemic heart diseases | 1054 (2.1) |
| Hypertensive diseases | 1012 (2.1) |
| Cerebrovascular diseases | 729 (1.5) |
| Diseases of arteries, arterioles and capillaries | 367 (0.8) |
| Pulmonary heart disease / diseases of pulmonary circulation | 186 (0.4) |

found with the cardiovascular outcomes.^{17,18} The study on oral contraceptive use and stroke found no significant association with haemorrhagic or ischaemic stroke when examining use by status (never, former, current oral contraceptive use), duration of use or age at first use (Table 5).

Dietary factors

Several papers have used WLH data to examine a variety of dietary factors in relation to lifestyle-related diseases. These include a range of dietary patterns,^{19–26} acrylamide,²⁷ phytoestrogens,^{28,29} dietary fat,³⁰ fish,³¹ fruits/vegetables³² and coffee/tea and caffeine³³ consumption. Notably, the study on acrylamide and breast cancer was the first prospective cohort study to examine this association after the Swedish National Food Administration announced the alarming discovery of acrylamide in commonly consumed baked and fried foods.³⁴ The study in the WLH cohort showed no significantly increased risk across quintiles of

Table 5. Relative risk (RR) of fatal or non-fatal stroke, according to oral contraceptive (OC) use. Adapted from reference 18

| | N of subjects | Stroke cases | Age-adjusted RR | Multivariate adjusted RR ^a |
|----------------------------|---------------|--------------|-----------------|---------------------------------------|
| Ischaemic stroke | | | | |
| OC status | | | | |
| Never users | 7471 | 44 | 1.0 (Ref.) | 1.0 (Ref.) |
| Former users | 6794 | 20 | 0.9 (0.5–1.6) | 1.1 (0.6–2.0) |
| Current users | 31 464 | 129 | 0.9 (0.6–1.2) | 0.9 (0.6–1.4) |
| Duration of OC use | | | | |
| <5 years | 16 262 | 74 | 0.9 (0.6–1.3) | 1.0 (0.6–1.5) |
| 5–9 years | 10 568 | 24 | 0.5 (0.3–0.9) | 0.6 (0.4–1.2) |
| ≥10 years | 10 877 | 45 | 1.0 (0.6–1.4) | 1.2 (0.7–1.9) |
| <i>P</i> for trend | | | 0.43 | 0.77 |
| Age at first use of OC | | | | |
| <20 | 22 065 | 62 | 0.9 (0.6–1.3) | 0.9 (0.6–1.5) |
| 20–24 | 11 228 | 59 | 0.9 (0.6–1.3) | 1.0 (0.6–1.6) |
| 25–30 | 3212 | 17 | 0.8 (0.4–1.3) | 1.0 (0.5–1.8) |
| >30 | 1445 | 7 | 0.7 (0.3–1.6) | 1.1 (0.5–2.4) |
| <i>P</i> for trend | | | 0.25 | 0.97 |
| Haemorrhagic stroke | | | | |
| OC status | | | | |
| Never users | 7471 | 10 | 1.0 (Ref.) | 1.0 (Ref.) |
| Former users | 6794 | 3 | 0.6 (0.2–2.2) | 0.4 (0.1–2.1) |
| Current users | 31 464 | 59 | 1.7 (0.9–3.3) | 1.6 (0.8–3.2) |
| Duration of OC use | | | | |
| <5 years | 16 262 | 31 | 1.7 (0.8–3.5) | 1.4 (0.7–3.0) |
| 5–9 years | 10 568 | 14 | 1.4 (0.6–3.2) | 1.5 (0.7–3.6) |
| ≥10 years | 10 877 | 17 | 1.6 (0.7–3.5) | 1.6 (0.7–3.6) |
| <i>P</i> for trend | | | 0.44 | 0.30 |
| Age at first use of OC | | | | |
| <20 | 22 065 | 30 | 2.0 (0.9–4.2) | 2.0 (0.9–4.4) |
| 20–24 | 11 228 | 19 | 1.2 (0.6–2.6) | 1.1 (0.5–2.4) |
| 25–30 | 3212 | 5 | 1.0 (0.3–2.9) | 0.9 (0.3–2.9) |
| >30 | 1445 | 6 | 2.7 (1.0–7.5) | 2.3 (0.8–6.8) |
| <i>P</i> for trend | | | 0.28 | 0.46 |

^aAdjusted for BMI, education, alcohol, smoking status, pack-years, physical activity, high blood pressure and diabetes

acrylamide intake and no association with specific foods identified as a source of acrylamide, such as fried potatoes, coffee or crisp bread²⁷ (Figure 2).

Sun / ultraviolet light exposure

The WHL study has detailed information on sun and ultraviolet light exposure and sensitivity. This has resulted in a number of papers, primarily on malignant melanoma,^{35,36} squamous cell skin cancer³⁷ and atypical nevi,^{38,39} showing a higher risk of both cancer types, especially with cumulative sun / ultraviolet light exposure. Furthermore, women with red hair colour, many nevi and high sun sensitivity experienced a further

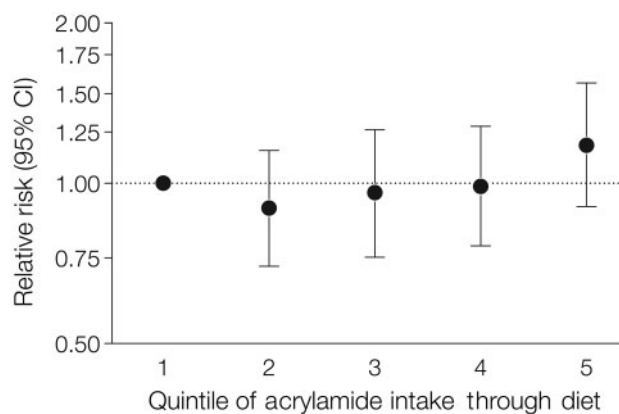


Figure 2. Quintiles of acrylamide intake throughout diet. Adapted from reference 27.

increased risk.^{35–37} In contrast, the studies found no association between sun / ultraviolet light exposure and breast cancer,⁴⁰ non-Hodgkin lymphoma⁴¹ or overall cancer.⁴² However, sun exposure was associated with lower overall mortality, whereas exposure to artificial ultraviolet light was associated with higher overall mortality.⁴³

Other notable exposures investigated in the WLH cohort include anthropometric measures in relation to breast cancer,^{44,45} and overall mortality,⁴⁶ cardiovascular disease,^{47,48} smoking^{49–52} and physical activity^{53–55} in relation to cancer / cardiovascular disease.

A summary of the most important findings with a specific focus on outcomes would entail a repetition of several of the above-mentioned findings. It should be mentioned, though, that the primary outcomes to which the WLH study has contributed epidemiological evidence include breast cancer, cardiovascular disease and overall mortality, as these are the outcomes with the highest incidence in the cohort and thus the largest statistical power to investigate epidemiological associations (Table 3). Other notable outcomes explored in the WLH cohort include other cancer types, primarily endometrial, ovarian^{16,33,45,50,55} and skin cancer.^{35–37}

What are the main strengths and weaknesses?

Strengths

The WLH cohort is a population-based, prospective cohort study with virtually complete follow-up of all participants. The large sample size provides the statistical power to investigate a range of outcomes. The relatively young age of the women at baseline meant that it took longer for the study to reach statistical power for a range of outcomes.

On the other hand, it enabled the investigation of a range of epidemiological associations in younger women that had previously been investigated primarily in middle-aged women. This enabled investigators to see if previously acknowledged associations were visible already in relatively young women, and entailed an intriguing new possibility for investigations, particularly for hormone-related exposures. The follow-up data add a temporal aspect to the exposure to hormonal factors, which may have changed over the course of follow-up due to things such as childbirth, breastfeeding, oral contraceptive use and menopausal status (see Table 2).

The long follow-up period that has passed since the collection of both baseline and follow-up data means that the number of cases has been growing, and with it the statistical power for a range of outcomes. A main strength of the cohort is that follow-up of the women is based on the unique national registration number, allowing linkage to a broad range of validated Swedish registries that include information on things such as cause and date of death, hospital discharge and drug use. Reporting is mandatory for several of these registries and, as mentioned previously, the validity of Swedish registries has generally been found to be high.^{11,13} The continuous follow-up of WLH participants through registries serves as a growing resource for research on the relationship between lifestyle and disease in young to middle-aged women over their lifetime, with a steadily accumulating number of cases.

Weaknesses

As is often the case with cohort studies, the WLH cohort suffers from potential healthy volunteer bias, as those with a serious illness or disability might be less likely to participate both at baseline and at follow-up. As shown in Table 1, the healthy volunteer bias is stronger in the selection of women who responded to the follow-up questionnaire (Table 1). This may affect the generalizability of findings from the WLH study. All information collected in the questionnaires is self-reported, and anthropometric information is self-measured, leaving room for potential information bias. Validation studies have been conducted on information collected in the food frequency questionnaire,⁵⁶ but no validation study has been done on the anthropometric and biological measures, and this should be kept in mind when using these data. As mentioned above, the relatively young age at enrolment entails a low power to investigate a number of outcomes, such as less common cancers and subgroups of cardiovascular disease. However, as the cohort ages and more person-years of follow-up accumulate, these numbers will increase,

allowing for more informative studies in the future. The last follow-up questionnaire was sent in 2003. As more than 10 years have now passed, it is likely that some women will have changed their exposure status. Although a third follow-up exposure assessment would contribute more up-to-date data, no such follow-up is planned at present. However, even though increasing exposure misclassification is a potential problem over an extended follow-up period, the induction time for the primary malignancies of interest in the present cohort (i.e. cancer and cardiovascular disease) is very long, often spanning decades, and the inclusion of women at a young age may have allowed us to capture exposures during the aetiologically relevant time period.

Finally, the Norwegian sister-cohort, NOWAC, has the added benefit of biological material,⁶ which is unfortunately not available for the WLH cohort. However, Sweden has unique opportunities to retrieve histopathological material, thus allowing some biological testing, for example detailed phenotypical characterization of tumours.

Can I get a hold of the data? Where can I find out more?

The data pertaining to the WLH are held at the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

Potential collaborators can read about the study and existing publications on the study webpage [<http://ki.se/en/meb/womens-lifestyle-and-health>]. As mentioned previously, an English translation of the two questionnaires is also available there. The page also contains contact information for the principal investigators, with whom potential ideas for collaboration should be discussed. In order to access WLH data, an analysis plan must be submitted and approved. Templates for applications to access the data are available upon request from Dr Elisabete Weiderpass [Elisabete.Weiderpass.Vainio@ki.se]. All collaborators should be able to cover their own study expenses, as the WLH study relies on ongoing grants that cover only approved/funded projects.

Profile in a nutshell

- The Women's Lifestyle and Health cohort is a prospective study, investigating the association between lifestyle (specifically hormonal factors) and, primarily, cancer / cardiovascular disease in young women.
- A total of 49 259 Swedish women aged 29–49 were included at baseline (1991–92).

- Women still living in Sweden in 2003 received a follow-up questionnaire; 73% of the available women (34 402) returned this. Furthermore, participants are followed up through Swedish registries on death, inpatient care and emigration.
- All women filled in a detailed questionnaire on hormonal/reproductive factors, disease history, anthropometry, occupation, lifestyle, personal characteristics, sun / ultra-violet exposure and an 80-item food frequency questionnaire.
- The data are held at the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, and are available to external scientists by application.

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