

# The Swedish mammography cohort and the cohort of Swedish men: study design and characteristics of two population-based longitudinal cohorts

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Study Design

## Abstract

### Introduction

The Swedish Mammography Cohort, established in 1987, and the Cohort of Swedish Men, established in 1997, are two ongoing population-based longitudinal cohorts designed to study dietary exposures in relation to chronic disease outcomes. This study discusses these two cohorts.

### Materials and methods

Information on dietary intake including alcohol and dietary supplements has been assessed by validated semi-quantitative food frequency questionnaires at multiple time points. Questionnaires have also collected information including anthropometric and physical activity measures across the life course, sleep habits, urine and bowel habits, family history of selected diseases, stress and social support. Annual linkage to multiple registries allows for up to date information on health status of all participants.

### Results

The mean ( $\pm$ SD) age and body mass index at cohort enrolment were 52.9 (9.8) years and 24.7 (3.9) kg/m<sup>2</sup> for the Swedish Mammography Cohort and 60.3 (9.7) years and 25.8 (3.4) kg/m<sup>2</sup> for the Cohort of Swedish Men. At baseline, 76% of Swedish Mammography Cohort participants and 82% of Cohort of Swedish Men participants were married. In 1997, 13% of Swedish Mammography

Cohort participants and 25% of Cohort of Swedish Men participants were current smokers, and 23% and 15% were regular users of dietary supplements, respectively.

### Conclusion

Recently, clinical sub-cohorts collecting more detailed information including blood, urine, and adipose tissue collection, dual energy X-ray absorptiometry scan, and a cognitive test phone interview have been established allowing for future in-depth analyses that examine health outcomes in an aging population.

### Introduction

The Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM) are two large population-based longitudinal cohorts established in Sweden. The SMC was established in 1987–1990 (together with a mammography screening program) with the aim to explore dietary exposures in relation to breast cancer risk and has since been expanded to assess risk of various health outcomes. The COSM was established 10 years later, in 1997, with the aim to explore diet and lifestyle in relation to chronic

**Table 1** Selected characteristics of participants in the Swedish Mammography Cohort (SMC) at baseline (1987) and follow-up (1997) and the Cohort of Swedish Men (COSM) at baseline (1997)<sup>1</sup>

Characteristics	Cohort/questionnaire year		
	SMC 1987	SMC 1997	COSM 1997
N	61,433	38,984	45,906
Age (years)	52.9 (9.8)	62.0 (9.3)	60.3 (9.7)
Married/living with partner (%)	76.3	—	82.4
Body mass index (kg/m <sup>2</sup> )	24.7 (3.9)	25.0 (4.0)	25.8 (3.4)
Height (cm)	164.1 (5.8)	164.3 (5.8)	177.2 (6.7)
Waist circumference (cm)	—	83.7 (10.8)	96.1 (11.7)
Hip circumference (cm)	—	102.7 (9.7)	101.9 (8.6)
Postmenopausal (%)	—	89.7	n/a
Age at menopause	—	49.6 (4.8)	n/a
Ever use of oral contraceptives (%)	—	43.8	n/a
Smoking status (%)			
Current	—	13.1	25.0
Past	—	33.0	38.9
Never	—	53.9	36.2
Regular user of dietary supplements (%)	—	22.8	14.9
Average hours of sleep per night	—	7.2 (1.1)	7.2 (1.1)

<sup>1</sup>Data represent mean (standard deviation) unless otherwise indicated.

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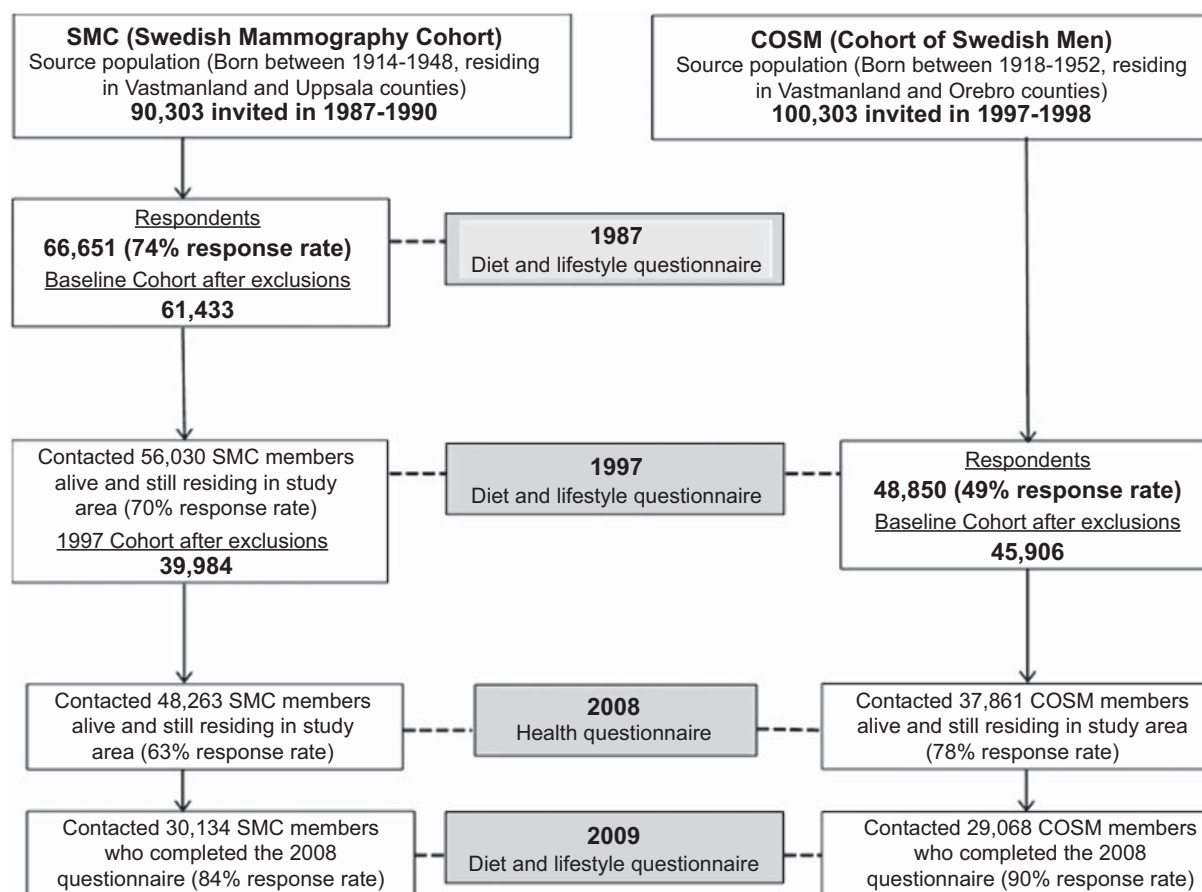
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**Figure 1:** Description of recruitment and data collection for the Swedish Mammography Cohort (SMC; 1987–2009) and the Cohort of Swedish Men (COSM; 1997–2009).

diseases. Since then, additional questionnaire data have been collected and sub-cohorts with biological specimens have been established making these cohorts a valuable resource for the scientific community. The aim of this study was to discuss the study design and characteristics of these two population-based longitudinal cohorts.

### Materials and methods

The SMC and the COSM are coordinated by the Unit of Nutritional Epidemiology within the Institute of Environmental Medicine at the Karolinska Institute, Stockholm, Sweden<sup>1</sup>. This work conforms to the values laid down in the Declaration of Helsinki (1964). The protocol of this study has been approved by the relevant ethical committee related to our institution in which it was performed.

All subjects gave full informed consent to participate in this study.

### SMC

#### Recruitment

From March 1987 to December 1990, all women living in Uppsala County of central Sweden and who were born in 1914 through 1948 ( $n = 48,517$ ) and all women living in the adjacent Västmanland County ( $n = 41,786$ ) who were born in 1917 through 1948 received an invitation by mail to participate in a population-based mammography screening program (Figure 1). The invitation included a six-page questionnaire that sought information on diet and alcohol intake (67-item Food Frequency Questionnaire [FFQ]), parity, age at first birth, family history of breast cancer, weight, height, education level and marital status. Women were

asked to return the completed questionnaire in-person at their mammogram appointment. Seventy-four per cent of women returned a completed questionnaire. After excluding those with an incorrect or missing national registration number, cancer diagnosis (except non-melanoma skin cancer) before baseline, implausible total energy intake (three standard deviations [SD] from the mean value for  $\log_e$ -transformed energy intake), those outside the age-range of 38–76 years, or other missing data, the final baseline cohort consisted of 61,433 women. Characteristics of the SMC at baseline are presented in Table 1.

#### 1997 SMC questionnaire

In the fall of 1997, a second extended questionnaire was sent to all SMC members ( $n = 56,030$ ) who were still alive and residing in the study area (Figure 1). The 1997 questionnaire collected

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information on diet and alcohol intake (96-item FFQ), dietary supplements, family history of cancer and myocardial infarction, age at menarche, history of oral contraceptive use, age at menopause, postmenopausal hormone use, disease diagnoses, body weight across the life course (birth weight through weight at age 80 years), current waist and hip circumferences, medication use and lifestyle factors including history of cigarette smoking, physical activity (at ages 15, 30, 50 and current) and sleep habits. The response rate for the 1997 questionnaire was 70%. After exclusion of those with an incorrect or missing national registration number the final 1997 cohort consisted of 38,984 participants. Characteristics of the SMC in 1997 are presented in Table 1. The SMC population is comparable to the general Swedish population with regards to age distribution, education level and body mass index (BMI; see Table 2).

### 2008 and 2009 SMC questionnaires

In 2008, a third questionnaire was sent to all cohort members ( $n = 48,263$ ) that had completed the 1987 FFQ (response rate 63%; Figure 1). The 2008 questionnaire collected information including general health status, disease diagnoses, current body weight, height, waist and hip circumferences, dental health, medication use, sleep habits, urine and bowel habits, family history of selected diseases, stress and social support. In 2009, a fourth questionnaire collecting information on diet and alcohol intake (132-item FFQ), dietary supplements, smoking, physical activity, and sun habits was sent to women who completed the 2008 questionnaire (84% response rate). The complete questionnaires can be accessed at: <http://ki.se/imm/nutrition-en>.<sup>1</sup>

### COSM

#### Recruitment

In the fall of 1997, all men born in 1918 through 1952 living in Västmanland and Örebro counties in central Sweden ( $n = 100,303$ ) received an invitation to

**Table 2 Comparison of the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM) with the Swedish population in 1997 for women aged 48–83 years and men aged 45–79 years, regarding age distribution, educational level and body mass index<sup>1</sup>**

Characteristics	SMC 1997	Female Population, aged 48–83 years, 1997 <sup>2</sup>	COSM 1997	Male Population aged 45–79 years, 1997 <sup>2</sup>
<b>Age groups, years</b>				
Total, n	38,984	1,633,520	45,906	1,594,952
45–49	—	—	15.9	19.5
48–54	28.5	27.6	—	—
50–54	—	—	18.8	20.8
55–59	17.9	15.0	15.9	15.6
60–64	14.5	12.7	13.1	12.5
65–69	13.5	12.7	14.1	11.6
70–74	12.4	12.7	12.4	10.8
75–79	10.1	12.1	9.9	9.2
80–83	2.9	7.3	—	—
<b>Education, ages 48–74 years<sup>3</sup></b>				
Total, n	33,914	1,316,743	41,382	144,585
≤12 years	78.9	78.7	82.3	77.1
>12 years	20.5	19.9	17.3	21.0
<b>Body Mass Index (&gt;25 kg/m<sup>2</sup>), by age groups<sup>4</sup></b>				
45–54	37.6	38.8	54.5	57.2
55–64	45.7	47.4	59.1	60.3
65–74	49.7	52.0	59.8	57.0
75–84	43.0	42.3	47.5	43.0

<sup>1</sup>All values are percentages unless otherwise indicated. Percentages may not add up due to missing values.  
<sup>2</sup>Data from Official Statistics Sweden (OSS).  
<sup>3</sup>Educational level reported are for those ≤74 years of age since data from OSS were not available for older ages.  
<sup>4</sup>Proportion of overweight (body mass index >25 kg/m<sup>2</sup>) people within each age group.

participate in the study, along with a self-administered questionnaire (Figure 1). The questionnaire, the same as used for the SMC in 1997, with the exception of some sex-specific questions, collected information on diet and alcohol intake (96-item FFQ), dietary supplements, family history of selected diseases, disease diagnoses, body weight across the life course, current waist and hip circumferences, medication use, lower urinary tract symptoms (International Prostate Symptom Score [I-PSS]) and lifestyle factors including history of cigarette smoking and physical activity (at ages 15, 30, 50 and current). A total of 48,850 (49%) men returned a completed questionnaire via mail.

After excluding those with an incorrect or missing national registration number, cancer diagnosis (except non-melanoma skin cancer) before baseline, death before baseline or other missing data the final baseline cohort consisted of 45,906 men. Characteristics of the COSM at baseline are presented in Table 1. The COSM population is comparable to the general Swedish population with regards to age distribution, education level and BMI (Table 2).

### 2008 and 2009 COSM questionnaires

In 2008, a second questionnaire was sent to all COSM members ( $n = 37,861$ ) who were still alive. The

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2008 questionnaire collected information including general health status, disease diagnoses, current weight, height, waist and hip circumferences, dental health, medication use, sleep habits, urine (I-PSS) and bowel habits, family history of selected diseases, stress and social support (78% response rate). In 2009, a third questionnaire collecting information on diet and alcohol intake (132-item FFQ), dietary supplements, smoking, physical activity, and sun habits was sent to men who completed the 2008 questionnaire (90% response rate). The complete questionnaires can be accessed at: <http://ki.se/imm/nutrition-en><sup>1</sup>.

### Questionnaire validation and reproducibility

Intake of nutrients and total energy were calculated from the food frequency questionnaires using food composition values obtained from the Swedish National Administration Database<sup>2</sup>. The reproducibility and validity of the FFQs used by the SMC and COSM have been assessed for foods, nutrients, dietary supplements, glycaemic index and glycaemic load by comparison with multiple 24-hour recall interviews and/or diet records<sup>3-7</sup>. In addition, FFQ-based estimates of total antioxidant capacity (TAC) have been validated with plasma TAC<sup>8</sup>, and fatty acid dietary intake has been validated with subcutaneous adipose tissue<sup>9</sup>. Exposure to environmental pollutants via foods has also been validated, including dietary polychlorinated biphenyls (PCB) exposure in relation to PCB concentrations in serum<sup>10</sup> and dietary cadmium exposure in relation to cadmium urine concentrations<sup>11</sup>. The physical activity questionnaire data have also been validated using 7-day activity records and accelerometers<sup>12</sup>.

### Follow-up of the cohorts through Registry Linkages

Using each participant's Swedish personal identity number<sup>13</sup>, the SMC and

the COSM are linked annually to multiple registries to ensure up to date information on all participants health status (Table 3). There are two main types of registries in Sweden, Health Data Registries and Quality Registries (national and regional)<sup>14,15</sup>.

### Health data registries

The Health Data Registries are the responsibility of the Department of Statistics, Monitoring and Evaluation (previously called the Epidemiological Centre) at the National Board of Health and Welfare (NBHW) and cover the entire Swedish population<sup>16</sup>. They include the National Patient Registry which encompasses the National Inpatient Registry (IPR; also called the Hospital Discharge Registry) and the National Outpatient Registry (OPR); the Cancer Registry; and the Prescribed Drug Registry<sup>14</sup>. The National IPR and OPR contain information about dates of admission and discharge, hospitals or clinics providing care, procedures, and main and secondary diagnoses (coded with international classification of disease codes)<sup>17</sup>. National coverage of the IPR has been 100% since 1987, while coverage of the OPR was ~80% in 2007. As of 2011, 99% of all somatic and psychiatric hospital discharges were registered in the IPR and a primary diagnosis was listed for 99% of all discharges. A review of the validity of the IPR by Ludvigsson et al. found positive predictive values (PPVs) of IPR diagnoses of 85–95% for most diagnoses, with PPVs for specific diagnoses of 98–100% for myocardial infarction, 82–97% for heart failure, 99% for stroke/transient ischemic attack, 87–96% for rheumatoid arthritis, 95–98% for hip fractures and 99% for acute pancreatitis<sup>17</sup>.

The Cancer Registry (established in 1958) contains basic information on all individuals diagnosed with cancer in Sweden including site of tumour, histological type (from 1993), and stage (from 2004). The Swedish National Cancer Registry

is estimated to be nearly 100% complete<sup>18</sup>. The Prescribed Drug Registry contains information about drugs dispensed under prescription at pharmacies (including dispensed amount, dosage, substance, brand name and formulation) and has been available for linkage since 2005<sup>19</sup>. The NBHW is also responsible for the Cause of Death Registry (established in 1961), which includes information about dates and causes of death. It is has been estimated that 93% of all deaths in Sweden are reported to the registry within 10 days and 100% are reported within 30 days<sup>13</sup>. These Health Data Registries are mandated by law and thus are an excellent source of medical information. In addition to the Health Data Registries described above, the NBHW also has a Care for the Elderly Registry and Persons with Impairments Registry, both established in 2007.

Besides the registries available through the NBHW, the government agency Statistics Sweden has information available regarding socio-economic status and demographics including level of education, income, employment/unemployment, early retirement due to disability, marital status, regional migration, immigrations and emigrations. Statistics Sweden is also responsible for the Multi-Generation Registry, through which family linkage (parents, siblings, children and cousins) and joint linkage with the NBHW may provide opportunities to study family history of diseases. The Multi-Generation Registry contains information on individuals born from 1932 and onwards.

### Quality registries

The National Quality Registries (approximately n = 73 receiving governmental funding as of June 2013) and regional quality registries contain more detailed clinical information than the Health Data Registries described above. These registries contain individualised data concerning

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**Table 3** Selected registries available for linkage to the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM)

Name of registry	Type of registry	Year established/coverage	Selected variables
National Patient Registry (National Inpatient Registry and National Outpatient Registry)	Health Data Registry	100% coverage of in-patients since 1987 80% coverage of out-patients in 2007	Dates of admission and discharge Hospital and clinic codes Procedures Main and secondary diagnoses
Cancer Registry	Health Data Registry	Established in 1958 Estimated to be nearly 100% complete	Site of tumour Histological type (from 1993) Stage (from 2004)
Prescribed Drug Registry	Health Data Registry	Available for linkage since 2005	Drugs dispensed under prescription Dispensed amount Dosage Substance Brand name Formulation
Cause of Death Registry	—	Established in 1961 100% complete	Date of death Cause(s) of death
National Prostate Cancer Registry	National Quality Registry	Established in 1996	TNM stage Gleason grade PSA values Treatment Prostate volume (from 2007) Type of prostatectomy (from 2007) Type of radiotherapy (from 2007)
National Breast Cancer Registry	National Quality Registry	Established in 2007*	Tumour characteristics (i.e. receptor status) TNM stage Grade Treatment Type of surgery Long- and short-term complications Waiting times for diagnosis and treatment
National Diabetes Registry	National Quality Registry	Established in 1996	Diabetes type Treatment Weight and height Abdominal circumference (from 2007) HbA1c Blood lipids (from 2002) Blood pressure S-creatinine (from 2002) Micro- and macro-albuminuria Physical activity (from 2007)

\*Prior to 2007 regional breast cancer quality registries allowed for coverage.

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All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.  
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patient problems, medical interventions and outcomes<sup>20</sup> with the vision of the quality registries to provide data needed for health care quality improvement<sup>14</sup>. Quality registries<sup>15</sup> that can be linked to the SMC and the COSM include those for cardiovascular disease (including Swedeheart, Heart Failure Registry [RiksSvikt], Vascular Registry in Sweden [Swedvasc], National Quality Registry for Stroke [Riks-Stroke]), National Diabetes Registry (NDR), cancer-specific quality registries (i.e. National Prostate Cancer Registry, National Breast Cancer Registry, Swedish Gynecology Registry, Swedish Colon Cancer Registry), Swedish Rheumatoid Arthritis Registry, Swedish Renal Registry and the Swedish National Cataract Registry.

Linkage to these quality registries provides detailed clinical data on a variety of conditions. For example, the NDR (established in 1996) contains a wealth of information on diabetes care including diabetes type, diabetes treatment, body weight, height, HbA1c, blood pressure, micro- and macroalbuminuria, blood lipids (from 2002), s-creatinine (from 2002), abdominal circumference (from 2007) and physical activity (from 2007). The National Prostate Cancer Registry (established in 1996) includes information on tumour-node-metastasis (TNM) stage, Gleason grade, prostate-specific antigen values and treatment. Additional data have been collected since 2007 including prostate volume, type of prostatectomy, and type of radiotherapy. The National Breast Cancer Registry (established in 2007) includes information on tumour characteristics (i.e. hormone receptor status), TNM stage, grade, treatment, type of surgery, long- and short-term complications and waiting-times for diagnosis and treatment. Prior to 2007, regional breast cancer quality registries allowed for coverage and have provided the SMC with data on tumour and

treatment characteristics since 1994 in Uppsala County and since 1997 in Västmanland County.

Through these Health Data Registry and Quality Registry linkages, diagnosis data (with data through 2011) for participants in the SMC and COSM have been obtained including cardiovascular disease (CVD;  $n = 31,509$ ; 8,004 MI; 9,321 stroke; 6,719 heart failure), type II diabetes ( $n = 15,200$ ), cancer ( $n = 20,319$ ; 3,608 breast; 3,969 prostate), fractures ( $n = 20,027$ ; 5,917 hip fractures), cataract extracts ( $n = 19,855$ ) and deaths ( $n = 28,726$ ; 8,441 cancer; 12,203 CVD; Table 4).

## Sub-cohorts

### SMC-Clinical

Recruitment 1: From 2003 through 2009, 8,311 women under age 85 and living in the town of Uppsala received a diet, lifestyle and physical activity questionnaire with an invitation to participate in a health examination. Sixty-five per cent of invited participants completed the questionnaire and 61% participated in the health examination which included weight, height, waist, hip, and blood pressure measurements, and a dual-energy X-ray absorptiometry scan ( $n = 5,022$ ). Blood, urine and adipose tissue were also collected at the health exam. Venous blood samples

**Table 4 Incident diagnoses of select health conditions and deaths in the Swedish Mammography Cohort (SMC; 1987–2011) and the Cohort of Swedish Men (COSM; 1998–2011)**

	Cohort	
	SMC ( $n = 61,433$ )	COSM ( $n = 45,906$ )
Cardiovascular disease (CVD)	19,638	11,871
Myocardial Infarction	4,171	3,833
Heart failure	3,762	2,957
Stroke	5,488	3,833
Cancer	11,532	8,787
Breast	3,597	11
Prostate	—	3,969
Colorectal	1,439	1,009
Lung	892	638
Endometrial	915	—
Ovarian	477	—
Pancreatic	308	165
Type II diabetes <sup>1</sup>	7,980	7,223
Rheumatoid arthritis	839	521
Fractures	14,767	5,260
Hip fractures	4,547	1,370
Cataract extractions	13,113	6,742
Kidney stones	851	1,297
Abdominal aortic aneurysm	353	1,005
Total deaths	17,181	11,545
CVD deaths	7,036	5,167
Cancer deaths	5,167	3,274

<sup>1</sup>Includes prevalent diagnoses reported on the 1997 questionnaire.

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were collected after a 12-hour overnight fast. Samples were immediately centrifuged and separated in a dark room, and stored at  $-80^{\circ}\text{C}$ .

A subset of these women completed an additional FFQ and physical activity questionnaire between 2004 and 2006 ( $n = 303$ ) and wore a physical activity monitor and completed a 7-day activity record ( $n = 151$ )<sup>12</sup>. A second subset of women ( $n = 116$ ), completed a questionnaire on sun exposure in conjunction with a blood sample collected during the winter months (January-March) and 100 of these women completed the same sun questionnaire and donated a blood sample during the summer (August and September)<sup>21</sup>.

A second health examination, biological sample collection and diet and lifestyle questionnaire, is planned for this clinical sub-cohort in November 2013.

Recruitment 2: From March 2012 to March 2013, 1,030 women in the SMC who were over age 85 and living in Uppsala County received an invitation to participate in a validated cognitive test phone interview<sup>22</sup>, complete a FFQ, and receive a home health examination ( $n = 627$ , 404 and 309 participants, respectively). The home health examination included weight, height, waist, hip and blood pressure measurements, blood, urine, adipose tissue and faecal sample collection, a physical function test and the Mini Mental State Examination.

#### COSM-Clinical

From May 2010 through June 2013, over 3,000 men in the COSM who were over age 75 and living in Västerås have received an invitation to participate in a validated cognitive phone interview<sup>22</sup>, complete an FFQ and a one-day food diary, and participate in a health examination. The health examination includes the same data collection as in the SMC-Clinical recruitment 2 described above. In addition, the wives of these men who are enrolled in the SMC have also

been invited to participate. Data collection for this clinical sub-cohort is ongoing and, to date, participation in the cognitive phone interview portion is over 83%.

#### Results

The mean ( $\pm$ SD) age and BMI at cohort enrolment were 52.9 (9.8) years and 24.7 (3.9)  $\text{kg}/\text{m}^2$  for the SMC and 60.3 (9.7) years and 25.8 (3.4)  $\text{kg}/\text{m}^2$  for the COSM. At baseline, 76% of SMC participants and 82% of COSM participants were married. In 1997, 13% of SMC participants and 25% of COSM participants were current smokers, and 23 and 15% were regular users of dietary supplements, respectively (Table 1).

#### Discussion

Research from the SMC and the COSM has resulted in over 200 scientific peer-reviewed publications. Important findings in the area of nutrition and cancer include protective associations observed between dietary folate intake and risk of ovarian cancer<sup>23</sup> and pancreatic cancer<sup>24</sup>; between magnesium intake and colorectal cancer risk<sup>25</sup>; between vitamin B6 intake and risk of colorectal cancer<sup>26</sup>; and between consumption of fatty fish and kidney cancer risk<sup>5</sup>. The SMC was the first to report a statistically significant interaction between alcohol consumption and hormone replacement therapy for the risk of oestrogen/progesterone-positive breast cancer, indicating that alcohol consumption is more harmful during hormone substitution<sup>27</sup>, and has observed an association between long-term dietary cadmium exposure (a proposed endocrine disruptor) and endometrial and breast cancer incidence<sup>11,28</sup>.

Beyond individual foods and nutrients we have also reported that the metabolic syndrome was associated with an increased risk of age-related cataracts<sup>29</sup> and that a combination of healthy dietary and lifestyle behaviours could prevent 77% of

myocardial infarctions among women in our study population<sup>30</sup>. In addition to these etiological studies, our cohorts have been the first to assess the validity of dietary questionnaire for estimates of glycaemic load<sup>7</sup>, total anti-oxidative capacity of consumed foods<sup>8</sup> and PCB exposure<sup>10</sup> and identified the saturated fatty acids penta-decanoic acid (15:0) and heptadecanoic acid (17:0) as valid biomarkers of long-term dairy fat intake<sup>9</sup>.

#### Conclusion

The SMC and the COSM are unique epidemiologic resources with their population-based design, high response rates, and multiple measures over a 20+ year period (1987–1997–2008/2009) for the SMC and 10+ year period for the COSM (1997–2008/2009). This allows for the examination of the associations between long-term diet and lifestyle factors and many different health outcomes. At present, very few prospective cohorts in Europe or the United States have repeated measurements and very few are representative of the whole population. In addition, the ability to link these cohorts to the extensive registry data available in Sweden is a strength that allows for near complete assessment of multiple health conditions. The recent and ongoing data collection in the clinical sub-cohorts will allow for future in-depth analyses that examine health outcomes in an aging population.

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