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Article title:

Disease history and risk of comorbidity in the life course of a woman: a comprehensive analysis of the Japan Nurses' Health Study baseline survey

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ABSTRACT

Objective:

To classify age at peak incidence of disease to examine the risk of comorbidities in the life course of a women.

Design:

A cross-sectional baseline survey of the Japan Nurses' Health Study.

Setting:

A nationwide prospective cohort study on the health of Japanese nurses. The baseline survey was conducted between 2001 and 2007 (n=49 927).

Main outcome measures:

Kaplan-Meier method and kernel smoothing technique were used to estimate age at peak incidence of 20 diseases from a survey of Japanese women. Incidence rate and peak incidence were estimated using and diseases whose peak incidence occurred before 45 years old or before the perimenopausal period were selected as early-onset diseases. The odds ratio (OR) was estimated to examine the risk of comorbidity between early-onset and other diseases.

Results:

The risk of comorbidity with early-onset diseases, which was significantly associated with Mantel-Haenszel OR (95% confidence interval) greater than 2.00, included ovarian cancer (3.65 [2.16 to 6.19]), endometrial cancer (2.40 [1.14 to 5.04]), cerebral infarction

(2.10 [1.15 to 3.85]) and a history of endometriosis; gastric cancer (3.69 [2.68 to 5.08]) and a history of anaemia; transient ischemic attack (3.06 [2.29 to 4.09]), osteoporosis (2.11 ([1.71 to 2.62]), cerebral infarction (2.04 [1.26 to 3.30]), angina pectoris (2.00 [1.49–2.67]) and a history of migraine; and colorectal cancer (2.31 [1.48 to 3.61]) and a history of uterine myoma. Four early-onset diseases (endometriosis, anaemia, migraine headache, and uterine myoma) were significantly correlated with one another.

Conclusions:

While there were significant associations between early-onset diseases, the women with a history of early-onset diseases had a higher risk of other diseases later in the life course. Understanding the history of early-onset diseases in women may help to reduce the subsequent risk of chronic diseases in later life.

Key words:

Comorbidity, women's health, life-course approach, early-onset diseases

ARTICLE SUMMARY

Article focus:

Women experience different diseases at different life stages according to reproductive health events. We attempted to classify age at peak incidence of disease and examined the risk of comorbidities.

Key messages:

The age at peak incidence of diseases in Japanese women varies in premenopausal, perimenopausal, and postmenopausal periods.

The associations found in this comprehensive study between early-onset diseases (those with a peak incidence before 45 years of age) and other diseases suggest that women with a history of early-onset diseases have a higher risk of other diseases later in the life course.

Understanding the history of early-onset diseases in women may help to reduce subsequent risk of chronic diseases in later life.

Strengths and limitations of this study:

Our study population, which was composed entirely of nurses, are likely to report such information more accurately than the general population because of their medical knowledge and clinical experience. We have no reason to suspect that the general population of women would differ in terms of risk of comorbidity between early-onset and other diseases later in the life course.

Introduction

Women experience various diseases at different life stages according to reproductive health-related events such as menarche and menopause.[1] In particular, postmenarchal and premenopausal women may develop oestrogen-dependent diseases such as endometriosis and uterine myoma.[2] While some diseases decline in frequency after menopause, others, such as hyperlipidaemia, occur more frequently, demonstrating that menopause represents a major transition event in a woman's life course.[3–5]

In women's health, it is important to understand how the history of gynaecological diseases that occur during premenopausal ages affects the risk of diseases that occur during perimenopausal or postmenopausal ages, from a life-course epidemiological point of view. A number of previous studies have highlighted the co-occurrence of gynaecological diseases with other disorders, such as the increased risk of ovarian cancer in women with endometriosis,[6] the association between blood oestrogen levels and migraine in women,[7 8] and the link between migraine and cardiovascular risk.[9] However, few epidemiological studies have comprehensively examined the risks of comorbidity between early-onset gynaecological diseases and other subsequent chronic diseases in later life.

The Japan Nurses' Health Study (JNHS) is a large-scale prospective cohort study investigating the effects of lifestyle, healthcare practices, and history of diseases on women's health.[10] In the cross-sectional baseline mail survey of the study, we

investigated the prevalence of past diagnosis and the age at first diagnosis for various diseases. The study population was designed for female registered nurses, public health nurses, and midwives who were at least 25 years of age and resident in Japan at the baseline survey. Nurses were preferred as the study population of such an epidemiological study because they were expected to report accurate medical information such as history of diseases. The objectives of this study were to classify diseases that occur frequently in women by identifying age at peak incidence and demonstrating their co-occurrence with other diseases based on the JNHS baseline data.

Methods

Survey participants

The study population comprised 49 927 female nurses who participated in the cross-sectional baseline survey of the JNHS, a nationwide prospective cohort study, between 2001 and 2007. The study population size was set to detect statistically an increase of 1.5 or more in relative risk in the 10-years follow-up phase of the JNHS. The details of the study plan and the sample size calculation have been presented elsewhere.[5, 10] Data were obtained from a self-administered postal questionnaire covering a wide range of health topics including lifestyle habits, disease history, reproductive health, and medication use.[10] We included 48 632 women whose responses to the questions of disease histories were completed. The JNHS study protocol was approved by the institutional

review boards of Gunma University and the National Institute of Public Health. Participants were informed of the study's purpose and procedures before recruitment. Written informed consent was provided before participation in the cohort study.

Medical history questionnaire

Disease history was ascertained using a questionnaire. The baseline survey investigated subjects' medical histories and obtained information on previous diagnoses, age at first diagnosis and treatment histories for a range of major medical disorders.

Diseases analysed and definition of comorbidity

We excluded from the analysis diseases that had a prevalence based on the diagnosis history of less than 0.001. We analysed 20 diseases including hypertension, angina pectoris, subarachnoid haemorrhage, cerebral infarction, transient ischemic attack (TIA), diabetes mellitus, thyroid disease, hypercholesterolemia, cholelithiasis, endometriosis, uterine myoma, cervical cancer, endometrial cancer, ovarian cancer, breast cancer, gastric cancer, colorectal cancer, osteoporosis, anaemia, and migraine. Comorbidity was defined as the co-occurrence of two diseases based on a subject's disease history at baseline survey regardless of the timing of disease onset.

Statistical analysis

We estimated the cumulative incidence and 95% confidence interval (95% CI) by the Kaplan-Meier survival analysis (product-limit method). In the survival analyses, we treated incidence at the age of first diagnosis as an event in women with a history of the disease and the observation was censored at the age recorded in the baseline survey in women without a history of the disease.[11] We estimated the age at peak incidence using the kernel smoothing method (Epanechnikov kernel) and defined early-onset diseases (diseases frequently occurred before the perimenopausal period) as those having a peak incidence less than 45 years of age.[12]

To examine the risk of comorbidity between the early-onset diseases and other diseases, odds ratios (ORs) and 95% CIs were calculated. A statistical analysis was conducted to examine homogeneity by the Breslow-Day test and to estimate a common odds ratio by the Mantel-Haenszel method between the two age groups, comparing the age at the baseline survey less than 50 years or 50 years or older. The crude ORs were also calculated as a sensitive analysis. Statistical significance was set at the 5% level (two-tailed) and no adjustments were made for multiplicity. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Subject characteristics

Of the 49 927 women who participated in the JNHS baseline survey, 48 632 who

responded to the questions of disease histories were included in the analysis. The average age (SD) at the baseline survey was 41.2 (7.9) years. The smoking prevalence in the study population was 17.2% (Table 1). In addition, 22.7% of respondents reported consuming alcoholic beverages more than three times per week. Most women, 32 642 (67.1%), were married at the baseline survey and 32 295 (66.4%) were parous. Only 6086 women (12.5%) were postmenopausal. The average reported age at menopause (SD) in the postmenopausal women was 49.1 (4.4) years.

Incidence of past diagnosis by disease

The cumulative incidences estimated by the Kaplan-Meier method at 30, 40, 50, and 60 years of age are shown in Table 2. The high cumulative incidence at 50 years of age, around the mean age at menopause, was 29.0% for anaemia, 18.9% for uterine myoma, 13.0% for hypercholesterolemia, 10.7% for migraine headache, 9.0% for hypertension, 7.4% for endometriosis, and 6.0% for thyroid disease.

According to the age at peak incidence of disease estimated by kernel smoothing, the early-onset diseases that had a peak of incidence before 45 years of age (before the perimenopausal period) were endometriosis (36.0 years), anaemia (36.0 years), migraine headache (44.8 years), uterine myoma (44.8 years) and cervical cancer (44.8 years). Figure 1-a shows the kernel smoothing estimates of incidence for these early-onset diseases. The peak incidence of thyroid disease, breast cancer and cholelithiasis occurred

between 45 and 54 years old in the perimenopausal period (Figure 1-b). For the other 12 diseases (subarachnoid haemorrhage, TIA, endometrial cancer, diabetes mellitus, gastric cancer, cerebral infarction, ovarian cancer, colorectal cancer, angina pectoris, osteoporosis, hypertension, and hypercholesterolemia), the peak incidence occurred after 55 years of age or in the postmenopausal period (Table 2).

Comorbidity among early-onset diseases

The early-onset diseases were endometriosis, anaemia, migraine, uterine myoma and cervical cancer. Four early-onset diseases (endometriosis, anaemia, migraine headache, and uterine myoma) were significantly correlated with one another (Table 3). It is worth noting that the OR (95% CI) for comorbid endometriosis and uterine myoma was 4.47 (4.09–4.87).

Comorbidity of four early-onset diseases and other diseases

The study population was stratified by age at survey into two strata, less than 50 years and 50 years of age or older. Examination of ORs for homogeneity across strata using the Breslow-Day test revealed that the risk of comorbidity was statistically heterogeneous for hypertension and hypercholesterolemia in women with endometriosis, diabetes mellitus, osteoporosis, hypertension and hypercholesterolemia in women with anaemia, thyroid disease, diabetes mellitus, angina pectoris, hypertension and hypercholesterolemia in

women with uterine myoma (Table 3). In all of those comorbidities, the OR in the older age strata was lower than in the younger age strata. The strength of the association was diminished in the older strata. The only statistically negative association of anaemia and diabetes mellitus was also heterogeneous between age strata (Breslow-Day test: P=0.028), indicating the negative association was stronger in older strata, with the OR changing from 0.86 in <50 years to 0.54 in ≥50 years of age strata.

The Mantel-Haenszel common ORs (95% CI) greater than 2.00 for comorbid endometriosis were 3.65 (2.16–6.19), 2.40 (1.14–5.04) and 2.10 (1.15–3.85) for ovarian cancer, endometrial cancer and cerebral infarction, respectively. The Mantel-Haenszel common OR greater than 2.00 for comorbid anaemia was 3.69 (2.68–5.08) for gastric cancer. The Mantel-Haenszel common OR for comorbid anaemia and diabetes mellitus was significantly lower, 0.68 (0.56–0.84). The Mantel-Haenszel common ORs greater than 2.00 for comorbid migraine headache were 3.06 (2.29–4.09), 2.11 (1.71–2.62), 2.04 (1.26–3.30) and 2.00 (1.49–2.67) for TIA, osteoporosis, cerebral infarction and angina pectoris, respectively. The Mantel-Haenszel common OR greater than 2.00 for comorbid uterine myoma was 2.31 (1.48–3.61) for colorectal cancer only (Table 3).

The crude ORs without any stratification were estimated as a sensitive analysis. The similar estimates were obtained (data not shown).

Discussion

The age at peak incidence of diseases in Japanese women varies in premenopausal, perimenopausal, and postmenopausal periods. The early-onset diseases (those with a peak incidence before 45 years of age) were endometriosis, anaemia, migraine headache, uterine myoma and cervical cancer. The associations found in this comprehensive study between early-onset diseases and other diseases suggest that women with a history of early-onset diseases have a higher risk of other diseases later in the life course. Understanding the history of early-onset diseases in women may help to reduce subsequent risk of chronic diseases in later life.

For endometriosis, the estimated age at peak incidence was 36.0 years of age and the cumulative incidence at 50 years of age was 7.4%; thus endometriosis could be considered a common gynaecological disorder in relatively young women. Endometriosis is characterized by excessive growth of extra-uterine endometrial tissue, resulting in subsequent bleeding into the abdominal cavity and ovaries, and presenting with symptoms such as peritonitis and painful defecation or urination. While levels of high-sensitivity C-reactive protein (CRP), a marker of inflammation, have been found to be significantly higher in women with endometriosis,[13] other studies have reported an association between elevated blood levels of high-sensitivity CRP and ischemic stroke.[14] [15] Inflammation resulting from endometriosis may therefore also be linked with an increased risk of ischemic stroke. Our results suggest that endometriosis may increase the risk of cerebral infarction and TIA by triggering inflammation. The Mantel-Haenszel OR

(95% CI) for comorbid endometriosis and ovarian cancer was 3.65 (2.16–6.19), which supports the conclusions of a previous study that found that endometriosis increases the risk of developing ovarian cancer.[6]

Anaemia was found to have the higher cumulative incidence (29.0% at 50 years of age). Anaemia is highly prevalent among women and may be diagnosed following pregnancy or heavy menstrual bleeding caused by uterine myoma. In the present study, the peak incidence for anaemia occurred at 36.0 years of age. Our results imply that relatively young, premenopausal women are more susceptible to anaemia than older, postmenopausal women. Our results also suggest a strong association between anaemia and gastric cancer. While anaemia can occur because of gastrectomy,[16] pernicious anaemia is associated with an increased risk of gastric cancer.[17–19] The causal pathway, including a reverse effect, could not be determined because of the study's cross-sectional design. This study had a novel finding in that there was a significant negative association between anaemia and diabetes mellitus. Several studies have reported that body iron stores or elevated ferritin concentrations were associated with an increased risk of type 2 diabetes mellitus,[20 21] potentially supporting our finding of the negative association between anaemia and diabetes mellitus.

Age at incidence peak of migraine headache was 44.8 years. Several studies reported that migraine was associated with oestrogen levels,[7 8] and the incidence significantly increased from menarche onwards;[22 23] migraine also increased the risk of ischemic stroke

and cardiovascular disease.[9] The present study's findings of a significantly enhanced risk of TIA, cerebral infarction and angina pectoris in migraine sufferers appear to support this.

The cumulative incidence at 50 years of age of uterine myoma was 18.9%. Although uterine myoma is often asymptomatic, we diagnosed a number of participants with the condition after undergoing cancer screening or a prenatal test. Uterine myoma is associated with elevated body mass index (BMI)[24] and body fat percentage,[25] suggesting that uterine myoma may be associated with obesity. Obesity is also associated with an increased risk of colon cancer.[26 27] The Mantel-Haenszel OR of comorbid colorectal cancer was 2.31 (1.48–3.61) in this study, suggesting that obesity is a potential common risk factor for uterine myoma and colorectal cancer.

The estimated age at peak incidence of not only the early-onset diseases but also other diseases in this study revealed the nature of diseases in a woman's life course. The diseases included hypercholesterolemia, hypertension and osteoporosis, which occur more frequently among postmenopausal women over 60 years of age. The cumulative incidences at 60 years of age for hypercholesterolemia, hypertension and osteoporosis were 41.3%, 23.4% and 6.7%, respectively, and these diseases exhibited a marked increase in incidence after the perimenopausal period.

The peak incidence for breast cancer occurred at 50.0 years (Figure 1-b), indicating that Japanese women are more likely to develop the disease before menopause rather than

after the perimenopausal period. Our results suggest that, unlike women in Western countries where the incidence of breast cancer increases with age even after menopause,[28] the incidence among women in Japan and other Asian settings exhibits a bell-shaped pattern with a peak at 45–50 years.[29] Our findings therefore support the current consensus that the incidence of breast cancer in Japan is higher before menopause than after.

The present study has several limitations. Information on disease diagnosis was based on self-reporting, which may have led to a misclassification of diagnoses. However, nurses are likely to report such information more accurately than the general population because of their medical knowledge and clinical experience. In addition, our study population, which was composed entirely of nurses, was likely to exhibit different health behaviours and be exposed to different risk factors compared with the general Japanese population. Thus, our findings may not be generalizable to the national population, reducing the present study's external validity. However, we have no reason to suspect that the general population of women would differ in terms of risk of comorbidity between early-onset and other diseases later in the life course. Also, data on disease histories were collected retrospectively, so eligible women who had developed fatal diseases prior to the survey were unable to participate. This may have led to an underestimation of disease incidence. In addition, we were unable to determine the causal relationship between comorbidities because of the cross-sectional design. A further analysis of the JNHS cohort using follow-up data is needed to determine the causal relationships between these

comorbidities. Finally, women over the age of 60 years were underrepresented relative to other age groups in the study.

Conclusions

The early-onset diseases were endometriosis, anaemia, migraine headache, uterine myoma and cervical cancer. While there were significant associations between the early-onset diseases, women with a history of early-onset diseases had a higher risk of other diseases later in the life course. Understanding the history of early-onset diseases in women may help to reduce the subsequent risk of chronic diseases in later life. Further research based on follow-up studies is needed to clarify the risk associations between these diseases.

Competing interest:

The authors report no competing interest.

Contributorship statement:

K Nagai analysed the data and drafted the report. K Hayashi designed and initiated the study . K Nagai, K Hayashi, T Yasui, and K Katanoda contributed to interpretation and discussion of the data and writing of the report. K Nagai, K Hayashi, T Yasui, K Katanoda, H Iso, Y Kiyohara, A Wakatsuki, T Kubota, and H Mizunuma approved the final draft to be published and agreed to account for all aspects of the work in ensuring

that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data sharing statement:

No additional data available

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References

1. Mishra GD, Anderson D, Schoenaker DA, *et al.* InterLACE: a new international collaboration for a life course approach to women's reproductive health and chronic disease events. *Maturitas* 2013; 74: 235–40.
2. Missmer SA, Hankinson SE, Spiegelman D, Barber RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometirosis by demographic, anthropometric, and lifestyle factors. *Am J Epidemiol* 2004; 160: 784–96.
3. Yasui T, Matsui S, Tani A, Kunimi K, Yamamoto S, Irahara M. Androgen in postmenopausal women. *J Med Invest* 2012; 59: 12–27.
4. Lee JS, Hayashi K, Mishra G, Yasui T, Kubota T, Mizunuma H. Independent association between age at natural menopause and hypercholesterolemia, hypertension, and diabetes mellitus: Japan nurses' health study. *J Atheroscler Thromb* 2013; 20: 161-9.
5. Fujita T, Hayashi K, Katanoda K *et al*. Prevalence of diseases and statistical power of the Japan Nurses' Health Study. *Ind Health* 2007; 45: 687–84.
6. Aris A. Endometriosis–associated ovarian cancer: A ten–year cohort study of women living in the Estrie Region of Quebec, Canada. *J Ovarian Res* 2010; 3:2.
7. MacGregor EA. Oestrogen and attacks of migraine with and without aura. *Lancet Neurol* 2004; 3: 354–61.

8. Brandes JL. The influence of estrogen on migraine: a systematic review. *JAMA* 2006; 295: 1824–30.

9. Bigal ME, Kurth T, Santanello N *et al*. Migraine and cardiovascular disease: a population-based study. *Neurology* 2010; 74: 628–35.

10. Hayashi K, Mizunuma H, Fujita T *et al*. Design of the Japan Nurses' Health Study: a prospective occupational cohort study of women's health in Japan. *Ind Health* 2007; 45: 679–86.

11. Hosmer DW, Lemeshow S, May S. Applied survival analysis: regression modeling of time-to-event data. 2nd edition. New Jersey. John Wiley & Sons; 2008, p16‑66.

12. Allison PD. Survival analysis using SAS: a practical guide 2nd edition. Cary, NC: SAS Institute Inc.; 2010, p29‑70.

13. Kinugasa S, Shinohara K, Wakatsuki A. Increased asymmetric dimethylarginine and enhanced inflammation are associated with impaired vascular reactivity in women with endometriosis. *Atherosclerosis* 2011; 219: 784–8.

14. Makita S, Nakamura M, Satoh K *et al*. Serum C-reactive protein levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population. *Atherosclerosis* 2009; 204: 234–8.

15. Chei CL, Yamagishi K, Kitamura A *et al*. C-reactive protein levels and risk of stroke and its subtype in Japanese: The Circulatory Risk in Communities Study (CIRCS). *Atherosclerosis* 2011; 217: 187–93.

16. Lim CH, Kim SW, Kim WC *et al*. Anemia after gastrectomy for early gastric cancer: Long-term follow-up observational study. *World J Gastroenterol* 2012; 18: 6114–9.

17. Mellemkjaer L, Gridley G, Møller H *et al*. Pernicious anaemia and cancer risk in Denmark. *Br J Cancer* 1996; 73: 998–1000.

18. Ye W, Nyrén O. Risk of cancers of the oesophagus and stomach by histology or subsite in patients hospitalised for pernicious anaemia. *Gut* 2003; 52: 938–41.

19. Vannella L, Lahner E, Osborn J, Annibale B. Systematic review: gastric cancer incidence in pernicious anaemia. *Aliment Pharmacol Ther* 2013; 37: 375–82.

20. Jiang R, Mason JE, Meigs JB, Ma J, Rifai N, Hu FB. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *JAMA* 2004; 291: 711–7.

21. Sun L, Franco OH, Hu FB *et al*. Ferritin concentrations, metabolic syndrome, and type 2 diabetes in middle-aged and elderly Chinese. *J Clin Endocrinol Metab* 2008; 93: 4690–6.

22. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache* 2001; 41:646–57.

23. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *JAMA* 1992; 267:64–9.

24. Takeda T, Sakata M, Isobe A *et al*. Relationship between metabolic syndrome and

uterine leiomyomas: a case-control study. *Gynecol Obstet Invest* 2008; 66: 14–7.

25. Sato F, Nishi M, Kudo R, Miyake H. Body fat distribution and uterine leiomyomas. *J Epidemiol* 1998; 8: 176–80.

26. Harriss DJ, Atkinson G, George K *et al*; C-CLEAR group. Lifestyle factors and colorectal cancer risk (1): systematic review and meta-analysis of associations with body mass index. *Colorectal Dis* 2009; 11: 547–63.

27. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. *Am J Clin Nutr* 2007; 86: 556–65.

28. Matsuno RK, Anderson WF, Yamamoto S *et al*. Early- and late-onset breast cancer types among women in the United States and Japan. *Cancer Epidemiol Biomarkers Prev* 2007; 16: 1437–42.

29. Toi M, Ohashi Y, Seow A et al. The Breast Cancer Working Group presentation was divided into three sections: the epidemiology, pathology and treatment of breast cancer. *Jpn J Clin Oncol* 2010; 40 Suppl 1: i13–18

Figure legend

Figure 1-a. Kernel-smoothing estimates of incidence for early-onset diseases that the peak occurred before 45 years old.

Figure 1-b Kernel-smoothing estimates of incidence for diseases that the peak occurred between 45 and 54 years old.

Table 1. Characteristics of study population at baseline survey.

Characteristics	N	Proportion
Age (year)		
<30	938	1.9%
30-34	11 174	23.0%
35-39	10 163	20.9%
40-44	9 656	19.9%
45-49	8 155	16.8%
50-54	5 929	12.2%
55-59	2 217	4.6%
60-64	339	0.7%
65≤	61	0.1%
Smoking status		
Non-smoker	33 918	69.7%
Current smoker	8 388	17.2%
Ex-smoker	5 648	11.6%
Missing	678	1.4%
Alcohol intake		
Non-drinker	14 224	29.2%
< 3day / week	20 391	41.9%
≥ 3day / week	11 024	22.7%
Missing	2 993	6.2%
Marital status		
Unmarried	11 633	23.9%
Married	32 642	67.1%
Divorced	2 850	5.9%
Separated / Widowed	980	2.0%
Missing	527	1.1%
Pregnancy		
Never	12 786	26.3%
Ever	33 618	69.1%
Missing	2 228	4.6%
Delivery		
Never	14 328	29.5%
Ever	32 295	66.4%
Missing	2 009	4.1%
Menopause status		
Pre-menopause	40 010	82.3%
Post-menopause	6 086	12.5%
Unknown	1 947	4.0%
Missing	589	1.2%

Table 2. Incidence peak and cumulative incidence for Kaplan-Meier estimate.

	Incidence peak¶ [%]	Age at incidence peak [years]	Cumulative incidence [%] 30 years K-M estimate	30 years 95% CI	40 years K-M estimate	40 years 95% CI	50 years K-M estimate	50 years 95% CI	60 years K-M estimate	60 years 95% CI
Endometriosis	0.25	36.0	2.19	2.07 to 2.33	4.91	4.70 to 5.12	7.36	7.06 to 7.67	7.76	7.41 to 8.12
Anaemia	0.85	36.0	12.4	12.1 to 12.7	19.2	18.8 to 19.5	29.0	28.5 to 29.6	31.8	31.1 to 32.6
Migraine headache	0.32	44.8	4.51	4.32 to 4.70	7.68	7.43 to 7.93	10.7	10.3 to 11.1	12.8	12.2 to 13.5
Uterine myoma	1.11	44.8	1.22	1.12 to 1.32	6.81	6.56 to 7.07	18.9	18.3 to 19.4	22.9	22.1 to 23.7
Cervical cancer	0.04	44.8	0.09	0.06 to 0.12	0.57	0.50 to 0.65	1.11	0.98 to 1.25	1.37	1.13 to 1.65
Thyroid disease	0.26	49.2	1.60	1.49 to 1.71	3.41	3.24 to 3.59	6.00	5.71 to 6.31	9.39	8.64 to 10.2
Breast cancer	0.10	50.0	0.04	0.03 to 0.06	0.33	0.27 to 0.39	1.50	1.33 to 1.70	2.72	2.20 to 3.37
Cholelithiasis	0.23	52.2	0.44	0.38 to 0.50	1.42	1.30 to 1.54	3.26	3.03 to 3.50	6.15	5.42 to 6.96
Subarachnoid haemorrhage	0.03	55.1	0.01	0.01 to 0.03	0.05	0.03 to 0.08	0.17	0.12 to 0.24	0.44	0.27 to 0.74
Transient ischemic attack	0.07	55.1	0.14	0.11 to 0.18	0.29	0.24 to 0.35	0.66	0.56 to 0.77	1.50	1.10 to 2.04
Endometrial cancer	0.02	55.9	0.00	0.00 to 0.01	0.04	0.03 to 0.07	0.16	0.11 to 0.24	0.51	0.32 to 0.81
Diabetes mellitus	0.38	57.3	0.08	0.06 to 0.11	0.41	0.35 to 0.49	1.92	1.73 to 2.14	6.49	5.57 to 7.55
Gastric cancer	0.05	57.3	0.03	0.02 to 0.05	0.16	0.12 to 0.21	0.52	0.42 to 0.63	0.98	0.67 to 1.43
Cerebral infarction	0.11	58.8	0.02	0.01 to 0.03	0.06	0.04 to 0.10	0.28	0.21 to 0.37	1.36	0.95 to 1.94
Ovarian cancer	0.06	63.9	0.06	0.04 to 0.08	0.13	0.10 to 0.17	0.28	0.21 to 0.36	0.38	0.25 to 0.57
Colorectal cancer	0.14†	≥65*	0.01	0.00 to 0.02	0.04	0.03 to 0.07	0.34	0.26 to 0.45	0.97	0.70 to 1.34
Angina pectoris	0.56†	≥65*	0.04	0.03 to 0.06	0.20	0.16 to 0.25	0.99	0.85 to 1.15	3.03	2.46 to 3.74
Osteoporosis	2.23†	≥65*	0.07	0.05 to 0.09	0.26	0.21 to 0.32	1.18	1.03 to 1.35	6.73	5.73 to 7.89
Hypertension	3.86†	≥65*	0.36	0.31 to 0.42	1.74	1.61 to 1.88	9.05	8.62 to 9.49	23.4	21.9 to 25.0
Hypercholesterolemia	4.74†	≥65*	0.94	0.86 to 1.03	3.27	3.10 to 3.45	13.0	12.5 to 13.5	41.3	39.4 to 43.2

* Age at incidence peak was undetermined because age-specific incidence was hockey stick-shaped until age 65 years.

† Incidence at 65 years of age.

¶ Incidence peak was estimated by kernel-smoothing technique.

Table 3. Mantel-Haenszel common odds ratios (95% confidence interval) for comorbidities.

	Endometriosis				Anaemia				Migraine				Uterine myoma			
	MH OR	95% CI		*P* value for Breslow-Day test	MH OR	95% CI		*P* value for Breslow-Day test	MH OR	95% CI		*P* value for Breslow-Day test	MH OR	95% CI		*P* value for Breslow-Day test
Endometriosis					2.31	(2.14 - 2.50)		0.225	1.96	(1.77 to 2.17)		0.652	4.47	(4.09 to 4.87)		0.449
Anaemia	2.31	(2.14 to 2.50)		0.225					2.13	(2.01 to 2.27)		0.045	2.73	(2.57 to 2.90)		0.410
Migraine headache	1.96	(1.77 to 2.17)		0.652	2.13	(2.01 to 2.27)		0.045					1.30	(1.20 to 1.42)		0.246
Uterine myoma	4.47	(4.09 to 4.87)		0.449	2.73	(2.57 to 2.90)		0.410	1.30	(1.20 to 1.42)		0.246				
Cervical cancer	1.12	(0.74 to 1.69)		0.969	0.82	(0.64 to 1.06)		0.093	1.32	(0.98 to 1.78)		0.203	1.39	(1.04 to 1.85)		0.412
Thyroid disease	1.49	(1.27 to 1.75)		0.595	1.18	(1.07 to 1.31)		0.306	1.24	(1.09 to 1.41)		0.073	1.43	(1.27 to 1.61)		0.010
Breast cancer	1.34	(0.91 to 1.96)		0.272	0.76	(0.59 to 0.98)		0.212	0.82	(0.58 to 1.17)		0.061	1.54	(1.19 to 1.99)		0.119
Cholelithiasis	1.31	(1.04 to 1.65)		0.905	1.19	(1.04 to 1.36)		0.348	1.42	(1.20 to 1.69)		0.135	1.68	(1.44 to 1.95)		0.015
Subarachnoid haemorrhage	1.00	(0.31 to 3.22)		0.480	0.67	(0.32 to 1.38)		0.385	1.50	(0.70 to 3.21)		0.663	0.92	(0.41 to 2.05)		0.409
Transient ischemic attack	1.91	(1.26 to 2.90)		0.748	1.44	(1.09 to 1.90)		0.899	3.06	(2.29 to 4.09)		0.384	1.38	(0.99 to 1.94)		0.529
Endometrial cancer	2.40	(1.14 to 5.04)		0.632	1.20	(0.68 to 2.09)		0.110	1.97	(1.05 to 3.70)		0.634	0.78	(0.35 to 1.74)		0.678
Diabetes mellitus	1.09	(0.79 to 1.51)		0.128	0.68	(0.56 to 0.84)		0.028	0.99	(0.77 to 1.28)		0.451	1.45	(1.19 to 1.77)		<0.001
Gastric cancer	0.87	(0.43 to 1.78)		0.946	3.69	(2.68 to 5.08)		0.879	1.06	(0.65 to 1.74)		0.252	1.04	(0.66 to 1.63)		0.539
Cerebral infarction	2.10	(1.15 to 3.85)		0.447	0.89	(0.56 to 1.42)		0.987	2.04	(1.26 to 3.30)		0.581	1.39	(0.85 to 2.25)		0.120
Ovarian cancer	3.65	(2.16 to 6.19)		0.208	0.94	(0.58 to 1.53)		0.995	1.51	(0.85 to 2.66)		0.291	1.60	(0.93 to 2.76)		0.539
Colorectal cancer	1.59	(0.80 to 3.16)		0.594	1.56	(1.02 to 2.37)		0.506	1.78	(1.06 to 2.97)		0.618	2.31	(1.48 to 3.61)		0.384
Angina pectoris	1.55	(1.03 to 2.32)		0.093	1.12	(0.86 to 1.45)		0.170	2.00	(1.49 to 2.67)		0.283	1.45	(1.09 to 1.91)		<0.001
Osteoporosis	1.89	(1.43 to 2.51)		0.532	1.49	(1.24 to 1.80)		0.010	2.11	(1.71 to 2.62)		0.622	1.54	(1.24 to 1.90)		0.441
Hypertension	1.26	(1.07 to 1.47)		0.003	0.98	(0.90 to 1.08)		0.035	1.69	(1.52 to 1.90)		0.455	1.50	(1.35 to 1.66)		<0.001
Hypercholesterolemia	1.30	(1.15 to 1.47)		0.021	1.06	(0.98 to 1.14)		<0.001	1.35	(1.23 to 1.48)		0.237	1.36	(1.25 to 1.48)		<0.001

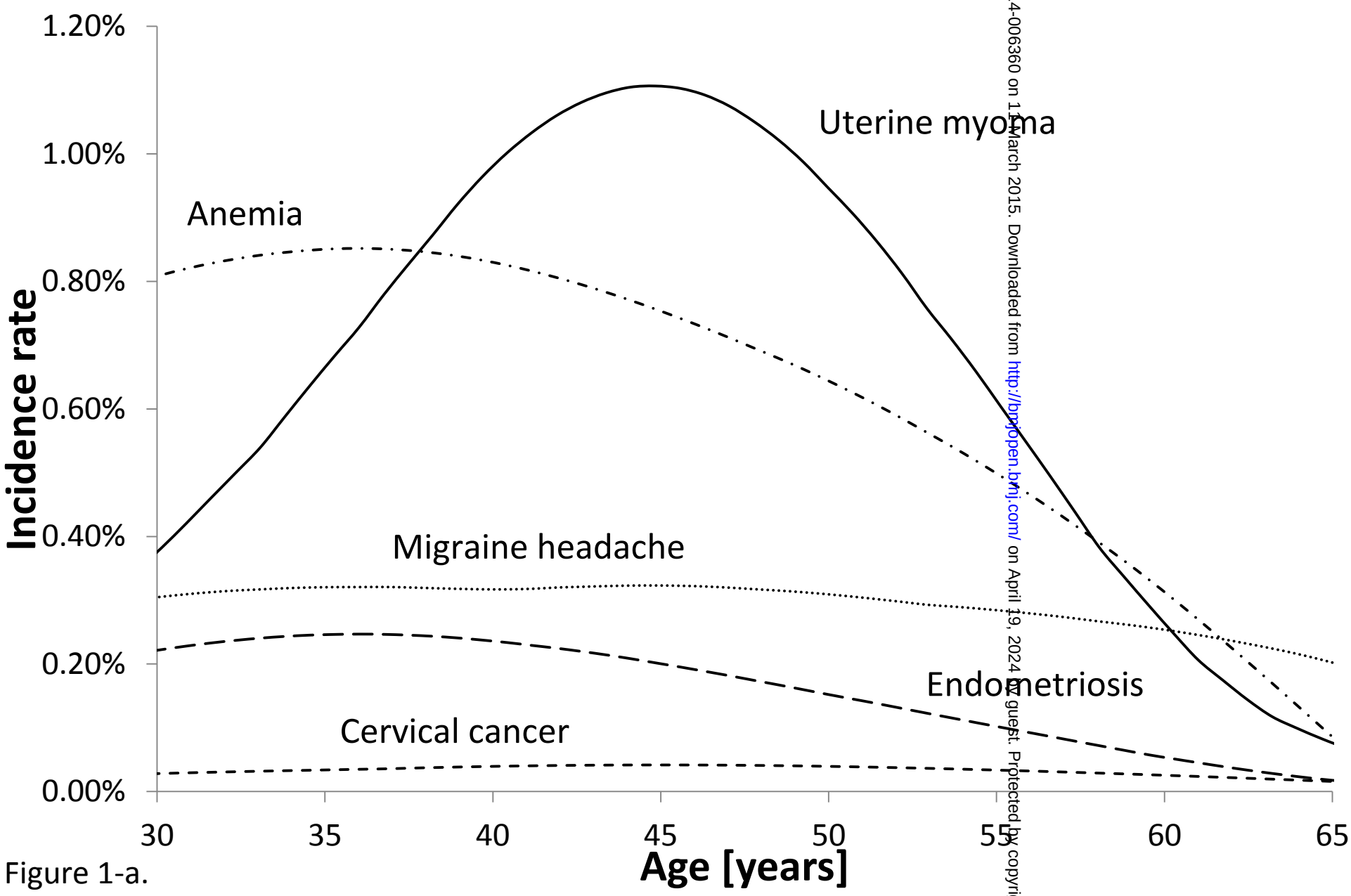

Figure 1-a.

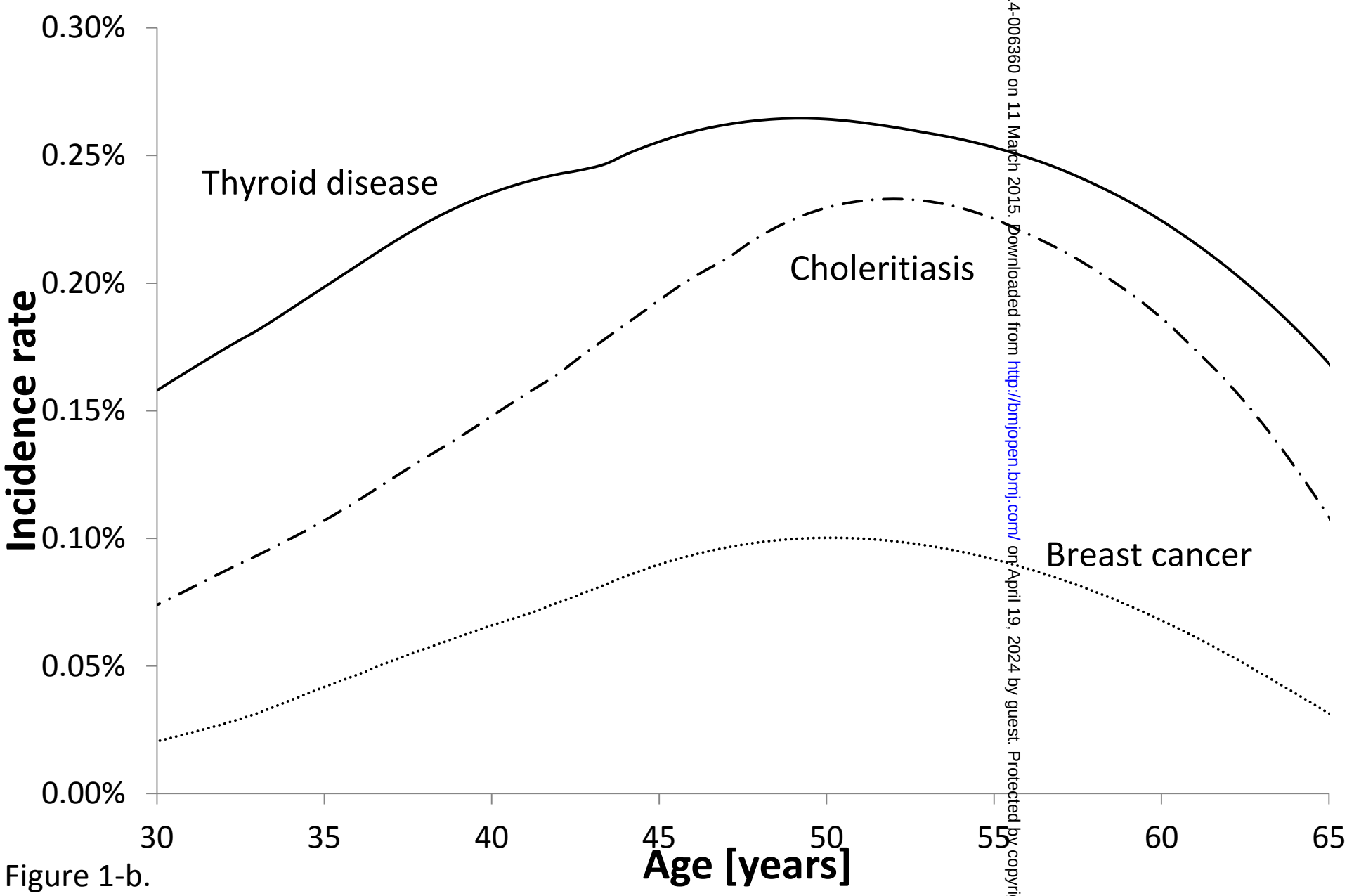

Figure 1-b.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No		Recommendation
Title and abstract	1☑	P.3 L.5-9	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		P.3 L.10-P.4 L.26	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	2☑	P.5 L.36-51	Explain the scientific background and rationale for the investigation being reported
Objectives	3☑	P.5 L.60-62	State specific objectives, including any prespecified hypotheses
Methods			
Study design	4☑	P.6 L.66-67	Present key elements of study design early in the paper
Setting	5☑	P.6 L.66-74	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6☑	P.6 L.73-74	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7☑	P.7 L.80-82, 85-92	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* ☑	P.7 L.80-82, 85-90	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9☑	P.6 L58-60, P.8 L.104-107	Describe any efforts to address potential sources of bias
Study size	10 ☑	P.6 L.68-70	Explain how the study size was arrived at
Quantitative variables	11 ☑	P.8 L.96-102	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 ☑	P.8 L.96-110	(*a*) Describe all statistical methods, including those used to control for confounding
		P.8 L.104-108	(*b*) Describe any methods used to examine subgroups and interactions
		P.6 L.73-74	(*c*) Explain how missing data were addressed
			(*d*) If applicable, describe analytical methods taking account of sampling strategy
		P.8 L.107-108	(*e*) Describe any sensitivity analyses
Results			

Participants	13* ☑	P.8 L.114- P.9 L.115	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		P.8 L.114- P.9 L.115	(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
Descriptive data	14* ☑	P.9 L.115-L.121, Table 1	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		Table 1	(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15* ☑	P.9 L124-128, Table 2	Report numbers of outcome events or summary measures
Main results	16 ☑	P.10 L.161-172, Table 3	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		P.9 L.129-139, P.11 L.161-170	(*b*) Report category boundaries when continuous variables were categorized
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 ☑	P.10 149-160 P.11 L.171-172	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18 ☑	P.12 L.175-180 P.14 L.226-232	Summarise key results with reference to study objectives
Limitations	19 ☑	P.15 L.240-256	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 ☑	P.12 L.178-182 P15. L.235-239	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 ☑	P.15 L.243-249	Discuss the generalisability (external validity) of the study results
Other information			
Funding	22 ☑	P.16 L.274-P.17 L.275	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Disease history and risk of comorbidity in the women's life course: a comprehensive analysis of the Japan Nurses' Health Study baseline survey

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Article title:

Disease history and risk of comorbidity in the women's life course: a comprehensive analysis of the Japan Nurses' Health Study baseline survey

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ABSTRACT

Objective:

To classify diseases based on age at peak incidence to identify the risk factors for later disease in the women's life course.

Design:

A cross-sectional baseline survey of participants in the Japan Nurses' Health Study.

Setting:

A nationwide, prospective cohort study on the health of Japanese nurses. The baseline survey was conducted between 2001 and 2007 (n=49 927).

Main outcome measures:

Age at peak incidence for 20 diseases from a survey of Japanese women was estimated using the Kaplan–Meier method with the kernel smoothing technique. The incidence rate and peak incidence for diseases whose peak incidence occurred before the age of 45 years or before the perimenopausal period were selected as early-onset diseases. The odds ratio (OR) and 95% confidence interval (95% CI) were estimated to examine the risk of comorbidity between early-onset and other diseases.

Results:

Four early-onset diseases (endometriosis, anaemia, migraine headache, and uterine myoma) were significantly correlated with one another. Late-onset diseases significantly associated (OR >2) with early-onset diseases included comorbid endometriosis with

ovarian cancer (3.65 [2.16–6.19]), endometrial cancer (2.40 [1.14–5.04]), and cerebral infarction (2.10 [1.15–3.85]); comorbid anaemia with gastric cancer (3.69 [2.68–5.08]); comorbid migraine with transient ischemic attack (3.06 [2.29–4.09]), osteoporosis (2.11 ([1.71–2.62]), cerebral infarction (2.04 [1.26–3.30]), and angina pectoris (2.00 [1.49–2.67]); and comorbid uterine myoma with colorectal cancer (2.31 [1.48–3.61]).

Conclusions:

While there were significant associations between four early-onset diseases, women with a history of one or more of the early-onset diseases had a higher risk of other diseases later in life course. Understanding the history of early-onset diseases in women may help reduce the subsequent risk of chronic diseases in later life.

Key words:

Comorbidity, women's health, life-course approach, early-onset diseases

ARTICLE SUMMARY

Article focus:

Women experience different diseases at different life stages according to reproductive health events. We attempted to classify the age at peak incidence of disease and examined the risk of comorbidities.

Key messages:

- The age at peak incidence of diseases in Japanese women varies in the premenopausal,

perimenopausal, and postmenopausal periods. The associations found in this comprehensive study between early-onset diseases (those with a peak incidence before 45 years of age) and other diseases suggest that women with a history of early-onset diseases have a higher risk of other diseases later in life course. Understanding the history of early-onset diseases in women may help reduce the subsequent risk of chronic diseases in later life.

Strengths and limitations of this study:

Our study population, which was composed entirely of nurses, are likely to report such information more accurately than the general population because of their medical knowledge and clinical experience. We have no reason to suspect that the general population of women would differ in terms of risk of comorbidity between early-onset and other diseases later in life course.

Introduction

Women experience various diseases at different life stages that correspond with reproductive health-related events such as menarche and menopause.[1] In particular, postmenarchal and premenopausal women may develop oestrogen-dependent diseases such as endometriosis and uterine myoma.[2] While some diseases decline in frequency after menopause, others, such as hyperlipidaemia, occur more frequently, demonstrating that menopause represents a major transition event in a woman's life course.[3–5]

In women's health, it is important to understand how the history of gynaecological diseases that occur during premenopausal ages affects the risk of diseases that occur during perimenopausal or postmenopausal ages, from a life-course epidemiological point of view. A number of previous studies have highlighted the co-occurrence of gynaecological diseases with other disorders, such as the increased risk of ovarian cancer in women with endometriosis,[6] the association between blood oestrogen levels and migraine in women,[7 8] and the link between migraine and cardiovascular risk.[9] However, few epidemiological studies have comprehensively examined the risks of comorbidity between early-onset gynaecological diseases and other subsequent chronic diseases in later life.

The Japan Nurses' Health Study (JNHS) is a large-scale prospective cohort study investigating the effects of lifestyle, healthcare practices, and history of diseases on women's health.[10] In the cross-sectional baseline mail survey of the study, we

investigated the prevalence of past diagnosis and age at first diagnosis for various diseases. The study population was designed for female registered nurses, public health nurses, and midwives who were at least 25 years of age and resident in Japan at the baseline survey. Nurses were preferred as the study population because they were expected to accurately report medical information such as disease history. The objectives of this study were to classify diseases that occur frequently in women by identifying age at peak incidence and demonstrating their co-occurrence with other diseases based on the JNHS baseline data.

Methods

Survey participants

The study population comprised 49 927 female nurses who participated between 2001 and 2007 in the cross-sectional baseline survey of the JNHS, a nationwide prospective cohort study. The size of the study population was set to detect an increase of 1.5 or more in relative risk in the 10-year follow-up phase of the JNHS. The details of the study plan and the sample size calculation have been presented elsewhere.[5, 10] Data were obtained from a self-administered postal questionnaire covering a range of health topics including lifestyle habits, disease history, reproductive health, and medication use.[10] We included 48 632 women whose responses to the questions on disease histories were completed. The JNHS study protocol was approved by the institutional review boards of Gunma

University and the National Institute of Public Health. Participants were informed of the study's purpose and procedures before recruitment. Written informed consent was provided before participation in the cohort study.

Medical history questionnaire

Disease history was ascertained using a questionnaire. The baseline survey investigated subjects' medical histories and obtained information on previous diagnoses, age at first diagnosis and treatment histories for a range of major medical disorders.

Diseases analysed and definition of comorbidity

We excluded diseases from the analysis that had a prevalence based on the diagnosis history of less than 0.001. We analysed 20 diseases including hypertension, angina pectoris, subarachnoid haemorrhage, cerebral infarction, transient ischemic attack (TIA), diabetes mellitus, thyroid disease, hypercholesterolemia, cholelithiasis, endometriosis, uterine myoma, cervical cancer, endometrial cancer, ovarian cancer, breast cancer, gastric cancer, colorectal cancer, osteoporosis, anaemia, and migraine. Comorbidity was defined as the co-occurrence of two diseases based on a subject's disease history at baseline survey regardless of the timing of disease onset.

Statistical analysis

We estimated the cumulative incidence and 95% confidence interval (95% CI) by Kaplan–Meier survival analysis (product-limit method). In the survival analyses, we treated incidence at the age of first diagnosis as an event in women with a history of the disease and the observation was censored at the age recorded in the baseline survey in women without a history of the disease.[11] We estimated the age at peak incidence using the kernel smoothing method (Epanechnikov kernel) and defined early-onset diseases (diseases occurring frequently before the perimenopausal period) as those having a peak incidence at less than 45 years of age.[12]

To examine the risk of comorbidity between the early-onset diseases and other diseases, odds ratios (ORs) and 95% CIs were calculated. A statistical analysis was conducted to examine homogeneity by the Breslow–Day test and to estimate a common odds ratio by the Mantel–Haenszel method between the two age groups (<50 years or ≥50 years). The crude ORs were also calculated as part of a sensitivity analysis. Statistical significance was set at the 5% level (two-tailed) and no adjustments were made for multiplicity. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Subject characteristics

Of the 49 927 women who participated in the JNHS baseline survey, 48 632 who responded to the questions of disease histories were included in the analysis. The average

age (SD) at the time of the baseline survey was 41.2 (7.9) years. The smoking prevalence in the study population was 17.2% (Table 1). In addition, 22.7% of respondents reported consuming alcoholic beverages more than three times per week. Most women, 32 642 (67.1%), were married at the time of the baseline survey and 32 295 (66.4%) were parous. Only 6086 women (12.5%) were postmenopausal. The average reported age at menopause (SD) in the postmenopausal women was 49.1 (4.4) years.

Incidence of past diagnosis by disease

The cumulative incidences estimated by the Kaplan–Meier method at 30, 40, 50, and 60 years of age are shown in Table 2. The high cumulative incidence at 50 years of age, around the mean age at menopause, was 29.0% for anaemia, 18.9% for uterine myoma, 13.0% for hypercholesterolemia, 10.7% for migraine headache, 9.0% for hypertension, 7.4% for endometriosis, and 6.0% for thyroid disease.

Based on the age at peak incidence of disease estimated by kernel smoothing, the early-onset diseases that had a peak of incidence before 45 years of age (before the perimenopausal period) were endometriosis (36.0 years), anaemia (36.0 years), migraine headache (44.8 years), uterine myoma (44.8 years) and cervical cancer (44.8 years). Figure 1-a shows the kernel smoothing estimates of incidence for these early-onset diseases. The peak incidence of thyroid disease, breast cancer and cholelithiasis occurred between 45 and 54 years of age, or in the perimenopausal period (Figure 1-b). For the

other 12 diseases (subarachnoid haemorrhage, TIA, endometrial cancer, diabetes mellitus, gastric cancer, cerebral infarction, ovarian cancer, colorectal cancer, angina pectoris, osteoporosis, hypertension, and hypercholesterolemia), the peak incidence occurred after 55 years of age, or in the postmenopausal period (Table 2).

Comorbidity among early-onset diseases

The early-onset diseases were endometriosis, anaemia, migraine, uterine myoma and cervical cancer. Four early-onset diseases (endometriosis, anaemia, migraine headache, and uterine myoma) were significantly correlated with one another (Table 3). It is worth noting that the OR (95% CI) for comorbid endometriosis and uterine myoma was 4.47 (4.09–4.87).

Comorbidity of four early-onset diseases and other diseases

The study population was stratified by age at survey into two strata, less than 50 years and 50 years of age or older. Examination of ORs for homogeneity across strata using the Breslow–Day test revealed that the risk of comorbidity was statistically heterogeneous for hypertension and hypercholesterolemia in women with endometriosis, diabetes mellitus, osteoporosis, hypertension and hypercholesterolemia in women with anaemia, thyroid disease, diabetes mellitus, angina pectoris, hypertension and hypercholesterolemia in women with uterine myoma (Table 3). In all of those comorbidities, the OR in the older

age stratum was lower than in the younger age stratum. The strength of the association was diminished in the older stratum. The only statistically negative association of anaemia and diabetes mellitus was also heterogeneous between age strata (Breslow–Day test: P=0.028), indicating that the negative association was stronger in the older stratum, with the OR changing from 0.86 in <50 years to 0.54 in the ≥50 years of age stratum.

The common ORs (95% CI) greater than 2.00 for comorbid endometriosis were 3.65 (2.16–6.19), 2.40 (1.14–5.04) and 2.10 (1.15–3.85) for ovarian cancer, endometrial cancer and cerebral infarction, respectively. The common OR greater than 2.00 for comorbid anaemia was 3.69 (2.68–5.08) for gastric cancer. The common OR for comorbid anaemia and diabetes mellitus was significantly lower, 0.68 (0.56–0.84). The common ORs greater than 2.00 for comorbid migraine headache were 3.06 (2.29–4.09), 2.11 (1.71–2.62), 2.04 (1.26–3.30) and 2.00 (1.49–2.67) for TIA, osteoporosis, cerebral infarction and angina pectoris, respectively. The common OR greater than 2.00 for comorbid uterine myoma was 2.31 (1.48–3.61) for colorectal cancer only (Table 3). The crude ORs without stratification were used in a sensitivity analysis. Similar estimates were obtained (data not shown).

Discussion

The age at peak incidence of diseases in Japanese women varies in the premenopausal, perimenopausal, and postmenopausal periods. The early-onset diseases (those with a peak

incidence before 45 years of age) were endometriosis, anaemia, migraine headache, uterine myoma and cervical cancer. The associations found in this comprehensive study between early-onset diseases and other diseases suggest that women with a history of early-onset diseases have a higher risk of other diseases later in life course. Understanding the history of early-onset diseases in women may help reduce any subsequent risk of chronic diseases in later life.

In this study, we observed a skewed age distribution because of the smaller sample size of participants aged 50 years or older. We stratified the study population by age at the time of the survey into two strata (<50 years and ≥50 years of age) and examined the homogeneity of ORs between the age groups. In addition, we estimated the common ORs between the two age groups instead of overall crude ORs to adjust for the skewed age distribution. However, statistical significance in the comorbidity of very late-onset diseases such as osteoporosis was unlikely because of the small sample size in the older age group.

For endometriosis, the estimated age at peak incidence was 36.0 years of age and the cumulative incidence at 50 years of age was 7.4%; thus, endometriosis could be considered a common gynaecological disorder in relatively young women. Endometriosis is characterized by excessive growth of extra-uterine endometrial tissue, resulting in subsequent bleeding into the abdominal cavity and ovaries, and presenting with symptoms such as peritonitis and painful defecation or urination. While levels of

high-sensitivity C-reactive protein (CRP), a marker of inflammation, have been found to be significantly higher in women with endometriosis,[13] other studies have reported an association between elevated blood levels of high-sensitivity CRP and ischemic stroke.[14] [15] Inflammation resulting from endometriosis may therefore also be linked with an increased risk of ischemic stroke. Our results suggest that endometriosis may increase the risk of cerebral infarction and TIA by triggering inflammation. The OR (95% CI) for comorbid endometriosis and ovarian cancer was 3.65 (2.16–6.19), which supports the conclusions of a previous study that found that endometriosis increases the risk of developing ovarian cancer.[6]

Anaemia was found to have the higher cumulative incidence (29.0% at 50 years of age). Anaemia is highly prevalent among women and may be diagnosed following pregnancy or heavy menstrual bleeding caused by uterine myoma. In the present study, the peak incidence for anaemia occurred at 36.0 years of age. Our results imply that relatively young, premenopausal women are more susceptible to anaemia than older, postmenopausal women. Our results also suggest a strong association between anaemia and gastric cancer. While anaemia can occur because of gastrectomy,[16] pernicious anaemia is associated with an increased risk of gastric cancer.[17–19] The causal pathway, including a reverse effect, could not be determined because of the study's cross-sectional design. This study had a novel finding in that there was a significant negative association between anaemia and diabetes mellitus. Several studies have reported that body iron

stores or elevated ferritin concentrations were associated with an increased risk of type 2 diabetes mellitus,[20 21] potentially supporting our finding of the negative association between anaemia and diabetes mellitus.

Age at incidence peak of migraine headache was 44.8 years. Several studies reported that migraine was associated with oestrogen levels,[7 8] and the incidence significantly increased from menarche onwards.[22 23] Migraine also increased the risk of ischemic stroke and cardiovascular disease in another study.[9] The present study's findings of a significantly enhanced risk of TIA, cerebral infarction and angina pectoris in migraine sufferers appear to support this.

The cumulative incidence at 50 years of age of uterine myoma was 18.9%. Although uterine myoma is often asymptomatic, we diagnosed a number of participants with the condition after undergoing cancer screening or a prenatal test. Uterine myoma is associated with elevated body mass index (BMI)[24] and body fat percentage,[25] suggesting that uterine myoma may be associated with obesity. Obesity is also associated with an increased risk of colon cancer.[26 27] The OR of comorbid colorectal cancer was 2.31 (1.48–3.61) in this study, suggesting that obesity is a potential common risk factor for uterine myoma and colorectal cancer.

The estimated age at peak incidence of not only the early-onset diseases, but also other diseases in this study, revealed the nature of diseases in a woman's life course. The diseases included hypercholesterolemia, hypertension and osteoporosis, which occur

more frequently among postmenopausal women over 60 years of age. The cumulative incidences at 60 years of age for hypercholesterolemia, hypertension and osteoporosis were 41.3%, 23.4% and 6.7%, respectively, and these diseases exhibited a marked increase in incidence after the perimenopausal period.

The peak incidence for breast cancer occurred at 50.0 years (Figure 1-b), indicating that Japanese women are more likely to develop the disease before menopause rather than after the perimenopausal period. Our results suggest that, unlike women in Western countries where the incidence of breast cancer increases with age even after menopause,[28] the incidence among women in Japan and other Asian settings exhibits a bell-shaped pattern with a peak at 45–50 years.[29] Our findings therefore support the current consensus that the incidence of breast cancer in Japan is higher before menopause than after.

The present study has several limitations. In this study, we defined disease onset as a diagnosis by a medical doctor that was reported on the self-administered questionnaire. Participants could only report a diagnosis; asymptomatic or undiagnosed diseases were excluded. Use of diagnoses rather than self-reported prevalence may affect correlation in some diseases. Information on disease diagnosis was based on self-reporting, which may have led to a misclassification of diagnoses. However, nurses are likely to report such information more accurately than the general population because of their medical knowledge and clinical experience. In addition, our study population, which was composed entirely of nurses, was likely to exhibit different health behaviours and be

exposed to different risk factors compared with the general Japanese population. Thus, our findings may not be generalizable to the national population, reducing the present study's external validity. However, we have no reason to suspect that the general population of women would differ in terms of risk of comorbidity between early-onset and other diseases later in life course. Additionally, data on disease histories were collected retrospectively, so only living participants were included in the survey. This may have led to an underestimation of disease incidence. Furthermore, we were unable to determine the causal relationship between comorbidities because of the cross-sectional design. Recall bias may have caused overestimation of ORs since sick people tend to report more about disease history. However, the participants were nurses we think that recall bias was minimized since they have medical knowledge and are more likely to have answered correctly. A further analysis of the JNHS cohort using follow-up data is needed to determine the causal relationships between these comorbidities. Finally, women over the age of 60 years were underrepresented relative to other age groups in the study.

Conclusions

While there were significant associations between the four early-onset diseases (endometriosis, anaemia, migraine headache, and uterine myoma), women with a history of early-onset diseases had a higher risk of other diseases later in life course. Understanding the history of early-onset diseases in women may help reduce the

subsequent risk of chronic diseases in later life. Further research based on follow-up studies is needed to clarify the cause–effect associations between these diseases.

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Contributorship statement:

K Nagai analysed the data and drafted the report. K Hayashi designed and initiated the study. K Nagai, K Hayashi, T Yasui, and K Katanoda contributed to interpretation and discussion of the data and writing of the report. K Nagai, K Hayashi, T Yasui, K Katanoda, H Iso, Y Kiyohara, A Wakatsuki, T Kubota, and H Mizunuma approved the final draft to be published and agreed to account for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interest:

The authors report no competing interest.

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Data sharing statement:

Not available.

References

1. Mishra GD, Anderson D, Schoenaker DA, *et al.* InterLACE: a new international collaboration for a life course approach to women's reproductive health and chronic disease events. *Maturitas* 2013; 74: 235–40.
2. Missmer SA, Hankinson SE, Spiegelman D, Barber RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometirosis by demographic, anthropometric, and lifestyle factors. *Am J Epidemiol* 2004; 160: 784–96.
3. Yasui T, Matsui S, Tani A, Kunimi K, Yamamoto S, Irahara M. Androgen in postmenopausal women. *J Med Invest* 2012; 59: 12–27.
4. Lee JS, Hayashi K, Mishra G, Yasui T, Kubota T, Mizunuma H. Independent association between age at natural menopause and hypercholesterolemia, hypertension, and diabetes mellitus: Japan nurses' health study. *J Atheroscler Thromb* 2013; 20: 161-9.
5. Fujita T, Hayashi K, Katanoda K *et al*. Prevalence of diseases and statistical power of the Japan Nurses' Health Study. *Ind Health* 2007; 45: 687–84.
6. Aris A. Endometriosis–associated ovarian cancer: A ten–year cohort study of women living in the Estrie Region of Quebec, Canada. *J Ovarian Res* 2010; 3:2.
7. MacGregor EA. Oestrogen and attacks of migraine with and without aura. *Lancet Neurol* 2004; 3: 354–61.

8. Brandes JL. The influence of estrogen on migraine: a systematic review. *JAMA* 2006; 295: 1824–30.

9. Bigal ME, Kurth T, Santanello N *et al*. Migraine and cardiovascular disease: a population-based study. *Neurology* 2010; 74: 628–35.

10. Hayashi K, Mizunuma H, Fujita T *et al*. Design of the Japan Nurses' Health Study: a prospective occupational cohort study of women's health in Japan. *Ind Health* 2007; 45: 679–86.

11. Hosmer DW, Lemeshow S, May S. Applied survival analysis: regression modeling of time-to-event data. 2nd edition. New Jersey. John Wiley & Sons; 2008, p16‑66.

12. Allison PD. Survival analysis using SAS: a practical guide 2nd edition. Cary, NC: SAS Institute Inc.; 2010, p29‑70.

13. Kinugasa S, Shinohara K, Wakatsuki A. Increased asymmetric dimethylarginine and enhanced inflammation are associated with impaired vascular reactivity in women with endometriosis. *Atherosclerosis* 2011; 219: 784–8.

14. Makita S, Nakamura M, Satoh K *et al*. Serum C-reactive protein levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population. *Atherosclerosis* 2009; 204: 234–8.

15. Chei CL, Yamagishi K, Kitamura A *et al*. C-reactive protein levels and risk of stroke and its subtype in Japanese: The Circulatory Risk in Communities Study (CIRCS). *Atherosclerosis* 2011; 217: 187–93.

16. Lim CH, Kim SW, Kim WC *et al*. Anemia after gastrectomy for early gastric cancer: Long-term follow-up observational study. *World J Gastroenterol* 2012; 18: 6114–9.

17. Mellemkjaer L, Gridley G, Møller H *et al*. Pernicious anaemia and cancer risk in Denmark. *Br J Cancer* 1996; 73: 998–1000.

18. Ye W, Nyrén O. Risk of cancers of the oesophagus and stomach by histology or subsite in patients hospitalised for pernicious anaemia. *Gut* 2003; 52: 938–41.

19. Vannella L, Lahner E, Osborn J, Annibale B. Systematic review: gastric cancer incidence in pernicious anaemia. *Aliment Pharmacol Ther* 2013; 37: 375–82.

20. Jiang R, Mason JE, Meigs JB, Ma J, Rifai N, Hu FB. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *JAMA* 2004; 291: 711–7.

21. Sun L, Franco OH, Hu FB *et al*. Ferritin concentrations, metabolic syndrome, and type 2 diabetes in middle-aged and elderly Chinese. *J Clin Endocrinol Metab* 2008; 93: 4690–6.

22. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache* 2001; 41:646–57.

23. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *JAMA* 1992; 267:64–9.

24. Takeda T, Sakata M, Isobe A *et al*. Relationship between metabolic syndrome and

uterine leiomyomas: a case-control study. *Gynecol Obstet Invest* 2008; 66: 14–7.

25. Sato F, Nishi M, Kudo R, Miyake H. Body fat distribution and uterine leiomyomas. *J Epidemiol* 1998; 8: 176–80.

26. Harriss DJ, Atkinson G, George K *et al*; C-CLEAR group. Lifestyle factors and colorectal cancer risk (1): systematic review and meta-analysis of associations with body mass index. *Colorectal Dis* 2009; 11: 547–63.

27. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. *Am J Clin Nutr* 2007; 86: 556–65.

28. Matsuno RK, Anderson WF, Yamamoto S *et al*. Early- and late-onset breast cancer types among women in the United States and Japan. *Cancer Epidemiol Biomarkers Prev* 2007; 16: 1437–42.

29. Toi M, Ohashi Y, Seow A et al. The Breast Cancer Working Group presentation was divided into three sections: the epidemiology, pathology and treatment of breast cancer. *Jpn J Clin Oncol* 2010; 40 Suppl 1: i13–18

Figure legend

Figure 1-a. Kernel-smoothing estimates of incidence for early-onset diseases with a peak incidence before 45 years of age.

Figure 1-b. Kernel-smoothing estimates of incidence for diseases with a peak incidence between 45 and 54 years of age.

Table 1. Characteristics of study population at baseline survey.

Characteristics	N	Proportion
Age (year)		
<30	938	1.9%
30-34	11 174	23.0%
35-39	10 163	20.9%
40-44	9 656	19.9%
45-49	8 155	16.8%
50-54	5 929	12.2%
55-59	2 217	4.6%
60-64	339	0.7%
65≤	61	0.1%
Smoking status		
Non-smoker	33 918	69.7%
Current smoker	8 388	17.2%
Ex-smoker	5 648	11.6%
Missing	678	1.4%
Alcohol intake		
Non-drinker	14 224	29.2%
< 3day / week	20 391	41.9%
≥ 3day / week	11 024	22.7%
Missing	2 993	6.2%
Marital status		
Unmarried	11 633	23.9%
Married	32 642	67.1%
Divorced	2 850	5.9%
Separated / Widowed	980	2.0%
Missing	527	1.1%
Pregnancy		
Never	12 786	26.3%
Ever	33 618	69.1%
Missing	2 228	4.6%
Delivery		
Never	14 328	29.5%
Ever	32 295	66.4%
Missing	2 009	4.1%
Menopause status		
Pre-menopause	40 010	82.3%
Post-menopause	6 086	12.5%
Unknown	1 947	4.0%
Missing	589	1.2%

Table 2. Incidence peak and cumulative incidence for Kaplan–Meier estimate.

	Incidence peak¶ [%]	Age at incidence peak [years]	Cumulative incidence [%] 30 years K-M estimate	30 years 95% CI	40 years K-M estimate	40 years 95% CI	50 years K-M estimate	50 years 95% CI	60 years K-M estimate	60 years 95% CI
Endometriosis	0.25	36.0	2.19	2.07 – 2.33	4.91	4.70 – 5.12	7.36	7.06 – 7.67	7.76	7.41 – 8.12
Anaemia	0.85	36.0	12.4	12.1 – 12.7	19.2	18.8 – 19.5	29.0	28.5 – 29.6	31.8	31.1 – 32.6
Migraine headache	0.32	44.8	4.51	4.32 – 4.70	7.68	7.43 – 7.93	10.7	10.3 – 11.1	12.8	12.2 – 13.5
Uterine myoma	1.11	44.8	1.22	1.12 – 1.32	6.81	6.56 – 7.07	18.9	18.3 – 19.4	22.9	22.1 – 23.7
Cervical cancer	0.04	44.8	0.09	0.06 – 0.12	0.57	0.50 – 0.65	1.11	0.98 – 1.25	1.37	1.13 – 1.65
Thyroid disease	0.26	49.2	1.60	1.49 – 1.71	3.41	3.24 – 3.59	6.00	5.71 – 6.31	9.39	8.64 – 10.2
Breast cancer	0.10	50.0	0.04	0.03 – 0.06	0.33	0.27 – 0.39	1.50	1.33 – 1.70	2.72	2.20 – 3.37
Cholelithiasis	0.23	52.2	0.44	0.38 – 0.50	1.42	1.30 – 1.54	3.26	3.03 – 3.50	6.15	5.42 – 6.96
Subarachnoid haemorrhage	0.03	55.1	0.01	0.01 – 0.03	0.05	0.03 – 0.08	0.17	0.12 – 0.24	0.44	0.27 – 0.74
Transient ischemic attack	0.07	55.1	0.14	0.11 – 0.18	0.29	0.24 – 0.35	0.66	0.56 – 0.77	1.50	1.10 – 2.04
Endometrial cancer	0.02	55.9	0.00	0.00 – 0.01	0.04	0.03 – 0.07	0.16	0.11 – 0.24	0.51	0.32 – 0.81
Diabetes mellitus	0.38	57.3	0.08	0.06 – 0.11	0.41	0.35 – 0.49	1.92	1.73 – 2.14	6.49	5.57 – 7.55
Gastric cancer	0.05	57.3	0.03	0.02 – 0.05	0.16	0.12 – 0.21	0.52	0.42 – 0.63	0.98	0.67 – 1.43
Cerebral infarction	0.11	58.8	0.02	0.01 – 0.03	0.06	0.04 – 0.10	0.28	0.21 – 0.37	1.36	0.95 – 1.94
Ovarian cancer	0.06	63.9	0.06	0.04 – 0.08	0.13	0.10 – 0.17	0.28	0.21 – 0.36	0.38	0.25 – 0.57
Colorectal cancer	0.14†	≥65*	0.01	0.00 – 0.02	0.04	0.03 – 0.07	0.34	0.26 – 0.45	0.97	0.70 – 1.34
Angina pectoris	0.56†	≥65*	0.04	0.03 – 0.06	0.20	0.16 – 0.25	0.99	0.85 – 1.15	3.03	2.46 – 3.74
Osteoporosis	2.23†	≥65*	0.07	0.05 – 0.09	0.26	0.21 – 0.32	1.18	1.03 – 1.35	6.73	5.73 – 7.89
Hypertension	3.86†	≥65*	0.36	0.31 – 0.42	1.74	1.61 – 1.88	9.05	8.62 – 9.49	23.4	21.9 – 25.0
Hypercholesterolemia	4.74†	≥65*	0.94	0.86 – 1.03	3.27	3.10 – 3.45	13.0	12.5 – 13.5	41.3	39.4 – 43.2

* Age at incidence peak was undetermined because age-specific incidence was hockey stick–shaped until age 65 years.

† Incidence at 65 years of age.

¶ Incidence peak was estimated by kernel–smoothing technique.

Table 3. Mantel–Haenszel common odds ratios (95% confidence interval) for comorbidities.

	Endometriosis			Anaemia			Migraine			Uterine myoma		
	MH OR	95% CI	*P* value for Breslow–Day test	MH OR	95% CI	*P* value for Breslow–Day test	MH OR	95% CI	*P* value for Breslow–Day test	MH OR	95% CI	*P* value for Breslow–Day test
Endometriosis				2.31	(2.14 - 2.50)	0.225	1.96	(1.77 – 2.17)	0.652	4.47	(4.09 – 4.87)	0.449
Anaemia	2.31	(2.14 – 2.50)	0.225				2.13	(2.01 – 2.27)	0.045	2.73	(2.57 – 2.90)	0.410
Migraine headache	1.96	(1.77 – 2.17)	0.652	2.13	(2.01 – 2.27)	0.045				1.30	(1.20 – 1.42)	0.246
Uterine myoma	4.47	(4.09 – 4.87)	0.449	2.73	(2.57 – 2.90)	0.410	1.30	(1.20 – 1.42)	0.246			
Cervical cancer	1.12	(0.74 – 1.69)	0.969	0.82	(0.64 – 1.06)	0.093	1.32	(0.98 – 1.78)	0.203	1.39	(1.04 – 1.85)	0.412
Thyroid disease	1.49	(1.27 – 1.75)	0.595	1.18	(1.07 – 1.31)	0.306	1.24	(1.09 – 1.41)	0.073	1.43	(1.27 – 1.61)	0.010
Breast cancer	1.34	(0.91 – 1.96)	0.272	0.76	(0.59 – 0.98)	0.212	0.82	(0.58 – 1.17)	0.061	1.54	(1.19 – 1.99)	0.119
Cholelithiasis	1.31	(1.04 – 1.65)	0.905	1.19	(1.04 – 1.36)	0.348	1.42	(1.20 – 1.69)	0.135	1.68	(1.44 – 1.95)	0.015
Subarachnoid haemorrhage	1.00	(0.31 – 3.22)	0.480	0.67	(0.32 – 1.38)	0.385	1.50	(0.70 – 3.21)	0.663	0.92	(0.41 – 2.05)	0.409
Transient ischemic attack	1.91	(1.26 – 2.90)	0.748	1.44	(1.09 – 1.90)	0.899	3.06	(2.29 – 4.09)	0.384	1.38	(0.99 – 1.94)	0.529
Endometrial cancer	2.40	(1.14 – 5.04)	0.632	1.20	(0.68 – 2.09)	0.110	1.97	(1.05 – 3.70)	0.634	0.78	(0.35 – 1.74)	0.678
Diabetes mellitus	1.09	(0.79 – 1.51)	0.128	0.68	(0.56 – 0.84)	0.028	0.99	(0.77 – 1.28)	0.451	1.45	(1.19 – 1.77)	<0.001
Gastric cancer	0.87	(0.43 – 1.78)	0.946	3.69	(2.68 – 5.08)	0.879	1.06	(0.65 – 1.74)	0.252	1.04	(0.66 – 1.63)	0.539
Cerebral infarction	2.10	(1.15 – 3.85)	0.447	0.89	(0.56 – 1.42)	0.987	2.04	(1.26 – 3.30)	0.581	1.39	(0.85 – 2.25)	0.120
Ovarian cancer	3.65	(2.16 – 6.19)	0.208	0.94	(0.58 – 1.53)	0.995	1.51	(0.85 – 2.66)	0.291	1.60	(0.93 – 2.76)	0.539
Colorectal cancer	1.59	(0.80 – 3.16)	0.594	1.56	(1.02 – 2.37)	0.506	1.78	(1.06 – 2.97)	0.618	2.31	(1.48 – 3.61)	0.384
Angina pectoris	1.55	(1.03 – 2.32)	0.093	1.12	(0.86 – 1.45)	0.170	2.00	(1.49 – 2.67)	0.283	1.45	(1.09 – 1.91)	<0.001
Osteoporosis	1.89	(1.43 – 2.51)	0.532	1.49	(1.24 – 1.80)	0.010	2.11	(1.71 – 2.62)	0.622	1.54	(1.24 – 1.90)	0.441
Hypertension	1.26	(1.07 – 1.47)	0.003	0.98	(0.90 – 1.08)	0.035	1.69	(1.52 – 1.90)	0.455	1.50	(1.35 – 1.66)	<0.001
Hypercholesterolemia	1.30	(1.15 – 1.47)	0.021	1.06	(0.98 – 1.14)	<0.001	1.35	(1.23 – 1.48)	0.237	1.36	(1.25 – 1.48)	<0.001

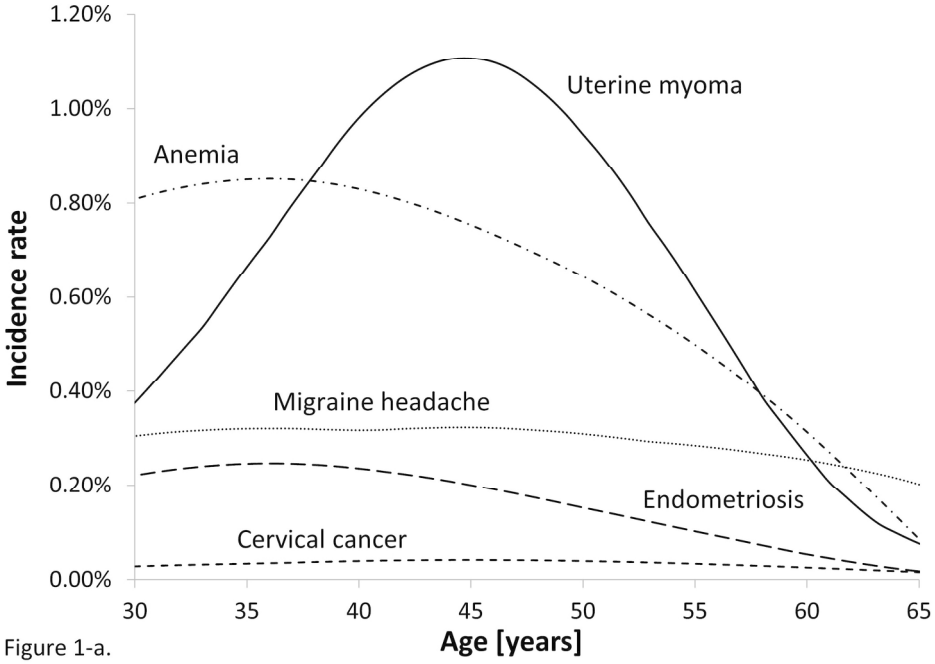

Figure 1-a.

Kernel-smoothing estimates of incidence for early-onset diseases with a peak incidence before 45 years of age.
190x142mm (300 x 300 DPI)

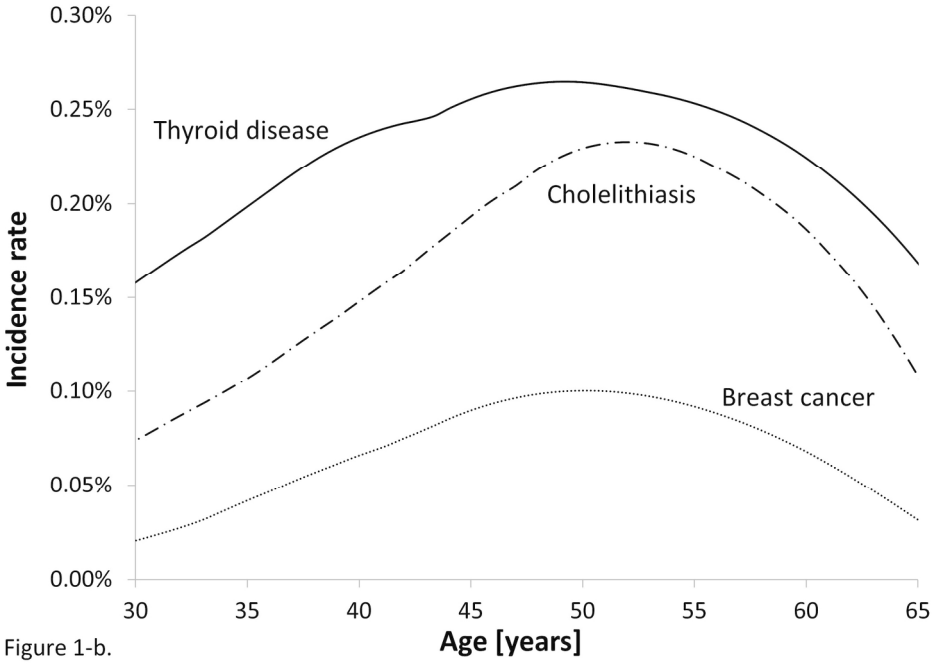

Figure 1-b.

Kernel-smoothing estimates of incidence for diseases with a peak incidence between 45 and 54 years of age.
190x142mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1☑	P.3 L.5-9 (*a*) Indicate the study's design with a commonly used term in the title or the abstract
		P.3 L.10-P.4 L.26 (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2☑	P.5 L.36-51 Explain the scientific background and rationale for the investigation being reported
Objectives	3☑	P.5 L.60-62 State specific objectives, including any prespecified hypotheses
Methods		
Study design	4☑	P.6 L.66-67 Present key elements of study design early in the paper
Setting	5☑	P.6 L.66-74 Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6☑	P.6 L.73-74 (*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7☑	P.7 L.80-82, 85-92 Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* ☑	P.7 L.80-82, 85-90 For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9☑	P.6 L58-60, P.8 L.104-107 Describe any efforts to address potential sources of bias
Study size	10 ☑	P.6 L.68-70 Explain how the study size was arrived at
Quantitative variables	11 ☑	P.8 L.96-102 Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 ☑	P.8 L.96-110 (*a*) Describe all statistical methods, including those used to control for confounding
		P.8 L.104-108 (*b*) Describe any methods used to examine subgroups and interactions
		P.6 L.73-74 (*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		P.8 L.107-108 (*e*) Describe any sensitivity analyses
Results		

Participants	13* ☑	P.8 L.114- P.9 L.115	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		P.8 L.114- P.9 L.115	(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
Descriptive data	14* ☑	P.9 L.115-L.121, Table 1	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		Table 1	(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15* ☑	P.9 L124-128, Table 2	Report numbers of outcome events or summary measures
Main results	16 ☑	P.10 L.161-172, Table 3	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		P.9 L.129-139, P.11 L.161-170	(*b*) Report category boundaries when continuous variables were categorized
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 ☑	P.10 149-160 P.11 L.171-172	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18 ☑	P.12 L.175-180 P.14 L.226-232	Summarise key results with reference to study objectives
Limitations	19 ☑	P.15 L.240-256	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 ☑	P.12 L.178-182 P15. L.235-239	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 ☑	P.15 L.243-249	Discuss the generalisability (external validity) of the study results
Other information			
Funding	22 ☑	P.16 L.274-P.17 L.275	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.