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Cardiovascular morbidity and mortality in postmenopausal women

In their forties and fifties, women have lower cardiovascular disease (CVD) rates than men of the same age (Tunstall-Pedoe et al., 1994). In their sixties, these lower rates persist but, as age increase, women catch up with men. This apparent protection from CVD has been attributed to high levels of circulating endogenous estrogens present in women rather than to chronological effect only (Bush, 1990). Thus, part of increase in CVD could be attributed to menopause. However, the effect on the cardiovascular risk (CVR) is only observed ten to fifteen years following menopause.

The WHO Monica Project is a 10-year study that monitors deaths due to coronary heart disease and acute myocardial infarction as well as coronary care and risk factors in men and women aged from 35 to 64 years in 38 defined communities from 21 countries. Data from this study are presented in the table 1.I.

Table 1.I : Age-standardized cardiovascular morbidity and mortality rates in all populations (age 35-64 years) registered in the WHO Monica project (according to Tunsdall-Pedoe et al., 1994)

	Cardiovascular morbidity (/100 000/year)	Cardiovascular fatality cases (%)
Male	465	49
Female	101	54

To assess the influence of menopause on the cardiovascular risk (CVR), several epidemiological studies have been selected. Only two prospective studies have been analysed concerning the risk of coronary heart disease (CHD) (Gordon et al., 1978 ; Colditz et al., 1987). To determine the importance of age at menopause onset, a review covering the results of seventeen studies published between 1953 and 1987 (Barrett-Connor and Bush, 1991) is commented on here and has been completed by the analysis of three additional reports (Van der Schouw et al., 1996 ; Rosenberg et al., 1981 ; Lapidus et al., 1985). Finally, the evolution of postmenopausal mortality has been consid-

ered in only one study, comparing cardiovascular mortality with all-cause mortality (Horiuchi, 1997).

Prospectives studies

The main features and results of five studies are described in tables 1.II and 1.III.

The Nurses' Health Study cohort considered 121 700 female registered nurses 30 to 55 years old ; 98 percent were white. In 1976, 116 258 of these women who were premenopausal or had a known history of menopause formed the population for the analysis of menopause and the risk of coronary heart disease (Colditz et al., 1987). A significant increase in the risk of coronary heart disease was observed among postmenopausal women with bilateral oophorectomy who had never received postmenopausal estrogen therapy. Natural menopause was not associated with a large increase in the risk of coronary heart disease. Similarly, among postmenopausal women who had undergone hysterectomy with unilateral oophorectomy, or hysterectomy without oophorectomy no material increase in the risk was observed.

The Framingham study considered a cohort of 2 873 Framingham women who were followed for 24 years. Beginning in 1948 these 2 873 women, then aged 29 through 62 years, were given a thorough cardiovascular examination. In 1978, Gordon et al. published a report based on data from the first 13 examinations. An increase in coronary heart disease incidence was found after both surgical and natural menopause, and this increase was not restricted to younger women with premature menopause. The findings suggest that the increase in coronary heart disease incidence occurs by a sudden escalation in risk at time of menopause.

A 12-year follow-up of 1 462 women initially aged 38-60 has been performed in Gothenburg, Sweden since 1968 (Lapidus et al., 1985). The 12-year incidences of the cardiovascular end-points studied are compared among women who reach menopause spontaneously at ages 40, 45 and 50. There were no statistical differences, but the risk ratios were increased for all the cardiovascular end-points studied except for « coronary ECG » irrespective of whether age 40, 45 or 50 years was defined as early menopause. Similar results were obtained when women with surgical menopause were included.

A cohort of 12 115 postmemopausal women living in Utrecht, Netherlands, aged 50-65 years was analysed by van der Schouw et al. in 1996 to investigate whether age at menopause was associated with cardiovascular risk. This analysis indicated that the risk of cardiovascular mortality was higher for women with early menopause than for those with late menopause. The extra risk of early menopause seemed to decrease with biological age (p for interaction 0.07) ; at biological age 60 the reduction in annual hazard was 3 %, but at age 80 there was no reduction.

Table 1.II : Cardiovascular morbidity or mortality in postmenopausal women

Authors	Population study design	N	Age range	Study period	Morbidity or mortality
Colditz et al. (1987)	US women prospective (Nurses'Health Study : NHS) CHD : non fatal MI, death due to CHD	121 700	30-55 in 1976 menopause: cessation of menses permanently	1976 to 1982	RR of CHD adjusted for age NatMp vs preMp: 1.2 (0.8-1.8) bilateral oophorectomy vs preMp : 2.2 (1.2-4.2)
Gordon et al. (1978)	Framingham prospective CHD : angina , coronary insufficiency, MI, death due to CHD	2 873	29- 62 in 1948 menopausal experience : 2-year interval	1948 to 1972	in age range 40 to 54 : RR of CHD adjusted for age NatMp vs preMp : 2.7 (p<0.001) Surgical vs preMp : 2.7 (p<0.01)
Witteman et al. (1989)	Netherlands cross-sectional atherosclerosis diagnosed by radiographic detection of calcified deposits in abdominal aorta	676	45-55		RR adjusted for NatMp vs preMp: 3.4 (1.2-9.7) Bilateral oophorectomy vs preMp : 5.5 (1.9-15.8)
Tunstall-Pedoe et al. (1994)	MONICA population-based registers fatal and nonfatal events	38 different populations	35-64	1985-1987	annual rate per 100 000 fatal and nonfatal among women < among men
Horiuchi (1997)	analysis of postmenopausal mortality acceleration LAR : life time aging rate	England and Wales, Italy, Japan, Netherlands, Spain, USA	35-80	1968-1978	postMp mortality acceleration, effects of CVD= more than 50% of the sex difference in all-cause mortality acceleration

Table 1.III : Age at menopause and cardiovascular morbidity and mortality

Authors	Population	N	Age range	Study period	Morbidity
Bengtsson (1973)	Sweden case-control	control : 578 angina pectoris : 29 MI: 57	50 and 54	1968-1969	women with MI : menopause earlier than controls (p<0.05)
Van der Schouw et al. (1996)	Netherlands prospective	12 115 women in breast screening project	50-65 at enrolment	1974-1994	each year menopause is delayed decreases the annual hazard of CV mortality by 2%
Lapidus et al. (1985)	Sweden prospective	1462	38-60 in 1968-69	1968-1980	for MI, angina, coronary ECG, stroke and overall mortality, no difference between early menopause and other women
Rosenberg (1981)	USA nurses case-control	age-matched control: 5 580 nonfatal MI: 279	<56	1976	RR bilateral oophorectomy before age 35 vs preMp : 7.2 (4.5-11.4) hysterectomy alone, NatMp: no confidence interval
Barrett-Connor & Bush (1991)	review	17 studies		1953-1987	increased risk of heart disease after bilateral oophorectomy, but differences inconsistent and often ns

The study by Horiuchi (1997) tested the hypothesis of a postmenopausal mortality acceleration. Mortality acceleration measured directly from vital statistics in selected countries was compared between males and females. The sex difference (female minus male) in mortality acceleration (SDMA) of all cardiovascular diseases combined is positive and their total effect is 85 % of all causes of SDMA in England and Wales, 69 % in Italy, and 56 % in Japan. These effects are large even in comparison with the proportion of all deaths in this age range that are due to cardiovascular diseases (50 % in England and Wales, 44 % in Italy and 45 % in Japan). The mortality increase of ischemic heart disease in this age range is substantially faster for females than for males. On the other hand, the extent of ischemic heart disease mortality acceleration does not differ notably between sexes. The other categories of cardiovascular disease (disease of arteries, arterioles and capillaries) generally exhibit greater female than male mortality acceleration. The acceleration starts around age 55, but it seems to take about a decade before the female rate of mortality increase overtakes the male rate of mortality increase. After about age 65, the female mortality level approaches the male level on the logarithmic scale, but never overtakes the male level, according to studies of centenarian mortality. It seems that the relative survival advantage of females over males is slowly attenuated at old ages but is not completely lost. The acceleration of female mortality appears to stop around age 75 in the populations of this study.

Cross-sectional and case-control studies

The methodology and results of these three studies are described in tables 1.II and 1.III. The Netherlands study was conducted in Zoetermeer, a suburb of The Hague between 1975 and 1978 (Witteman et al., 1989). In this study, 294 premenopausal and 319 postmenopausal women aged 45 to 55 were examined radiographically for calcified deposits in the abdominal aorta, which have been shown to represent intimal atherosclerosis. After adjustement for age and other indicators of cardiovascular risk, women with natural menopause had 3-4 times more risk of atherosclerosis than premenopausal women (95 % CI 1.2 to 9.7 ; p<0.005) ; women who had had bilateral oophorectomy had 5.5 times more risk (1.9 to 15.8 ; p<0.005). No excess risk of atherosclerosis was observed among women who had had hysterectomy without removal of both ovaries.

In the Nurses cohort, Rosenberg et al. (1981) evaluated the relation between age at menopause and nonfatal myocardial infarction (MI) among women under 56 years of age. The authors studied 279 women who had been hospitalized for MI and 5 580 control subjects selected from among 121 964 registered nurses. For each of the 279 cases, 20 control subjects were selected at random from those respondents without a history of MI who were born in the same year as the case subject and whose menopausal status at the date of

hospitalization for MI was known. Of the 279 MI cases, 44 % were postmenopausal at the time of MI compared with 33 % of 5 580 matched control subjects. Among women who became menopausal because of bilateral oophorectomy, the estimated relative risk of MI increased with decreasing age at menopause, and women who underwent bilateral oophorectomy before age 35 were estimed to have a risk of hospitalisation for MI approximately 7.2 times (95 % CI, 4.5 to 11.4) that of premenopausal women. Hysterectomy with preservation of at least one ovary was associated with a small increase in the risk of MI.

Bengtsson et al. (1973) retrospectively studied age at menopause in the Swedish female population from Göteborg, suffering from ischaemic heart diseases (IHD - 29 with angina pectoris and 57 with myocardial infarction) or presenting ECG changes suggesting IHD (23 women). Significantly more women with IHD were postmenopausal at 45-50 years than in the general population (578 control women). This study suggests an association between premature menopause and ischaemic heart diseases. However, all the women aged 47 or less were still menstruating at the time of their infarct, suggesting that menopause is not strictly necessary for the development of early myocardial infarction.

Critical analysis

As regards the connection between menopause and coronary heart diseases (CHD), only two prospective studies (Gordon et al., 1978 ; Colditz et al., 1987) have been selected and reviewed above. They are the only ones in which the effect of menopause was estimated after age adjustment (the risk of CHD is known to increase with this parameter). The results obtained in these two studies disagree ; only Gordon et al. (1978) observed a significant influence of natural menopause on the risk of CHD. In contrast, in these two cohorts, a relative risk (RR) of similar magnitude was found to be significantly associated with bilateral oophorectomy (2.2 and 2.7). The discrepancy between the results reported in the Framingham study and in the NHS (Nurses'Health Study) may be explained by differences in criteria used to estimate the onset of natural menopause. The coronary events taken into account also differ in these two studies : only non fatal myocardial infarction (MI) and death due to CHD are considered in the NHS study, while moderate forms of CHD are analysed by Gordon et al. Finally, because of their occupational status, nurses may have a healthier lifestyle and lower CHD risk level than the general population.

The MONICA population-based registers do not evaluate a potential association between menopause and CV mortality, because they do not consider hormonal status but only age (Tunsdall-Pedoe et al., 1994). Horiuchi (1997), using the model of the life time aging rate, reports a postmenopausal mortal-

ity acceleration, the consequences of CV diseases accounting for more than 50 % of the sex difference in the acceleration of all-cause mortality.

To ascertain the influence of age at menopause (early menopause) on CHD, all published studies have been considered, although the report of Van der Schouw et al. (1996) appears to be the most reliable. Barrett-Connor's review (Barrett-Connor and Bush, 1991) indicates that a number of results concerning the association of early menopause with the risk of heart disease are inconsistent and often not statistically significant. However, the prospective study performed in the Netherlands (Van der Schouw et al., 1996) shows that a delayed onset of menopause is associated with a decrease in cardiovascular mortality. Bilateral oophorectomy before age 35 is also reported as being linked to an increase in the RR of non-fatal MI.

To conclude, surgical menopause creates a clear-cut estrogen deprivation. Bilateral oophorectomy is followed by a clear increase in the CVD risk, while only a slight increase is observed following natural menopause. These results were obtained in two studies involving women living in the United States.

Another important question is to determine if age at menopause can influence the CVR enhancement. Early bilateral oophorectomy seems to be associated with an increase in the risk of non-fatal MI. Age at the onset of natural menopause is also of importance for CV mortality, as each year of delay seems to lower the risk by 2 %.

Finally, a study devoted to the relations between menopause and mortality (all causes and CV mortality) showed a postmenopausal mortality acceleration with an increase in CVD.

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