

## Cardiovascular risk factors in women

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Rates of CHD have been shown to be considerably higher in men than women in all countries where reliable prevalence data are available, including those countries with low rates of the disease, such as Japan (World Health Organization, 1989). In the UK, for women at any given age, the death rate for CHD is approximately equivalent to that seen in men 10 years earlier (Fig. 1). This earlier presentation in men means that CHD often occurs during a man's active middle years, with consequently greater social and economic impact on individuals and their families. These differences in age at occurrence have almost certainly contributed to the perception that CHD is a disease of men and one to which women are relatively resistant. Whilst it is certainly true that being female confers some protection against CHD, it is also true that CHD is a major cause of death in women, responsible for 23% of all female mortality and the major cause of premature death in women less than 60 years old (Office of Population Censuses and Surveys, 1993). It is also well established that women who suffer a myocardial infarct (MI) have a poorer prognosis than men. In the Framingham study, the 12-month mortality after MI was 45% for women and 20% for men (Kannel *et al.* 1979). This could be related to their greater age at occurrence or to the greater prevalence of factors such as diabetes or hypertension in women compared with men. It has also been shown that following an MI, women are less likely to be offered intensive drug and surgical therapy.

Others have suggested that the later occurrence and greater severity at first MI in women are due to differences in the biological processes involved (Walsh & Grady, 1995) and, for this reason, the assumption that cardiovascular risk factors are the same in men and women may be incorrect (Hulley *et al.* 1992). This question is difficult to address because much of the research into the causes, prevention and treatment of the disease has been conducted only in men and provides an inadequate basis for discriminating gender-specific risk factors in CHD.

### CARDIOVASCULAR RISK FACTORS

A large body of research evidence has established age, smoking, hypertension, raised blood cholesterol and obesity as risk factors in CHD (Table 1). More recently, research has concentrated on the role of haemostatic factors (Meade *et al.* 1986; Miller, 1986; Ernst, 1990) and on a collection of metabolic risk factors variously described under the terms 'metabolic syndrome' or 'syndrome X' (Reaven, 1988) or more recently as 'visceral fat syndrome' (Matsuzawa *et al.* 1993). Other risk factors, such as raised homocysteine levels (Genest *et al.* 1990) and poor antioxidant status (Duthie *et al.* 1993), have excited a great deal of interest because they have implications for our understanding of the mechanisms by which diet influences this disease.

One of the few prospective studies of CHD to have included mortality data for women as well as men was the Renfrew and Paisley study, which carried out a 15-year follow-up of 15 339 adults, including 8262 women, in a region of Scotland with very high mortality rates for CHD (Isles *et al.* 1992). This study, which evaluated only the major risk factors,

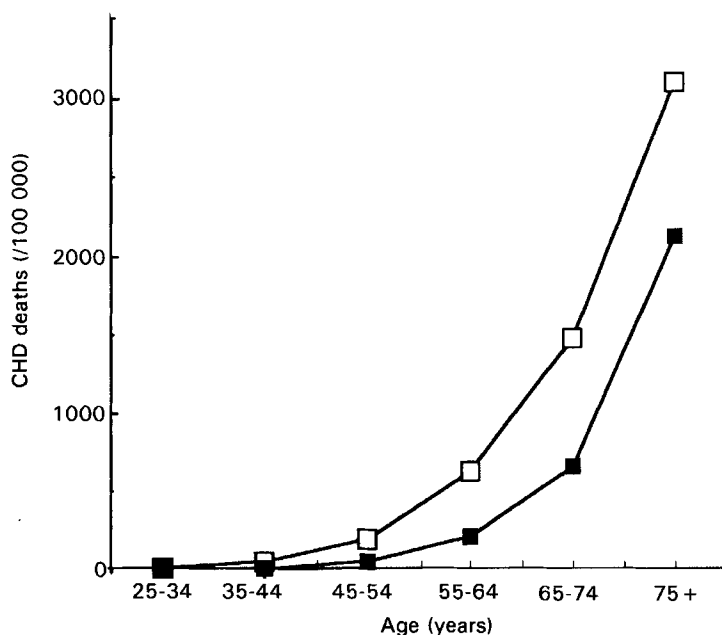


Fig. 1. Annual death rates from coronary heart disease in men (□) and women (■) in the UK; effects of age. (From World Health Organization, 1989.)

Table 1. Established and proposed risk factors for cardiovascular disease in men and women

Established	Proposed
Family history	Haemostatic:
Age	Fibrinogen
Smoking	Factor VII
Raised BP	Metabolic:
Raised cholesterol levels	HDL-cholesterol
	Triacylglycerols
	Insulin resistance
	LDL subtype distribution
	Central obesity
	Other:
	Homocysteine
	Antioxidant status

BP, blood pressure.

showed relative risks for blood pressure, cholesterol and smoking to be similar in men and women. However, the study also clearly showed that for varying levels of exposure of each of the risk factors, women had markedly lower rates of CHD mortality than men. The findings for blood cholesterol are of particular interest (Fig. 2), because in this population the mean cholesterol concentration for women was higher than that for the men, a finding which is consistent with data for the UK adult population in general (Gregory *et al.* 1990).

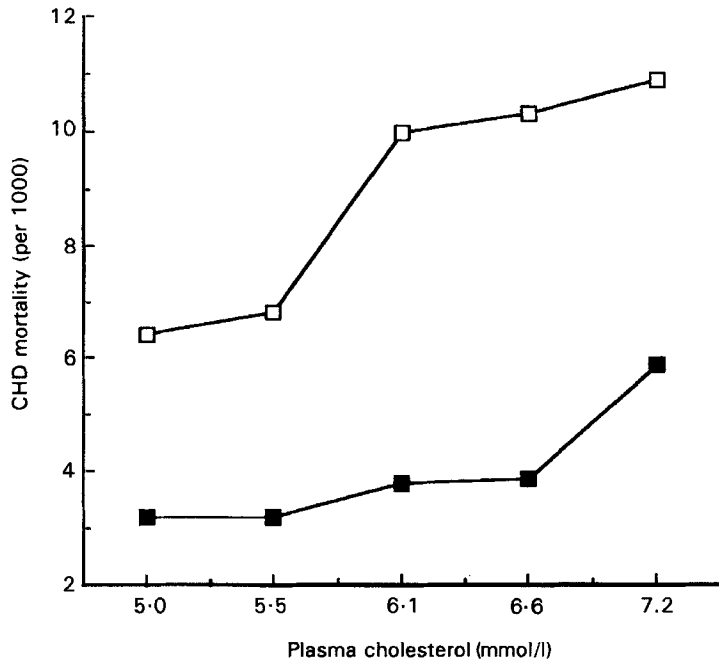


Fig. 2. Adjusted CHD mortality in deaths per 1000 patient years for men (□) and women (■) by quintile of cholesterol. (Redrawn from Isles *et al.* 1992.)

The findings from the Renfrew study suggest that women are relatively resistant to the adverse effects of established risk factors, and are consistent with the general observation that, despite greater prevalence of abnormal values for cholesterol, hypertension and obesity in women, attributable risks are far lower in the female than the male UK population.

#### METABOLIC RISK FACTORS

Evidence has begun to emerge which suggests that the lesser susceptibility of women to CHD may lie partly, but not exclusively, in their lower prevalence of metabolic risk factors (Table 1). In addition, studies conducted over the past 5 years have provided a clearer picture of the mechanism(s) by which insulin resistance and central obesity, the key characteristics of the metabolic syndrome, may be linked to the generation of an atherogenic lipid profile (Fig. 3) (Frayn & Coppack, 1992; Després & Lamarche, 1993; Frayn, 1993), of which a short summary is provided here. Fat deposited in the abdominal region is more metabolically active than fat deposited subcutaneously (Arner, 1995) and, therefore, it is proposed, releases greater amounts of non-esterified fatty acids directly into the portal vein (Bjorntorp, 1991), with consequent adverse effects on insulin clearance and degradation (Kissebah *et al.* 1988). This leads to a state of insulin-resistant hyperinsulinaemia with consequent stimulation, rather than the usual inhibition, of VLDL secretion (Howard *et al.* 1987; Wiggins & Gibbons, 1992). This adverse effect of increased VLDL output is added to by high circulating levels of chylomicron (CM) triacylglycerol which arises from impaired activity of insulin on adipose-tissue lipoprotein lipase (*EC*

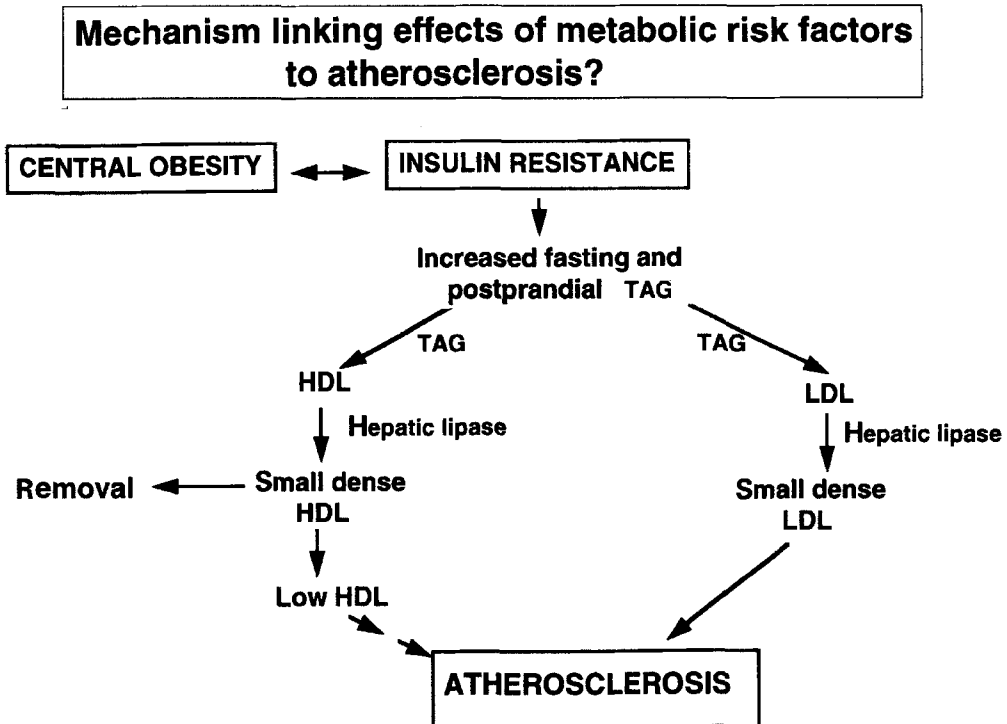


Fig. 3. Outline of proposed mechanism by which insulin resistance and central obesity may be linked to atherogenesis. TAG, triacylglycerols; lipase, EC 3.1.1.3.

3.1.1.34; Eckel, 1989; Jeppesen *et al.* 1995), and these increases in CM and VLDL particles are reflected in both elevated fasting and postprandial triacylglycerol concentrations. The presence of large numbers of triacylglycerol-containing particles results in neutral lipid exchange with transfer of triacylglycerol from CM and VLDL onto HDL and LDL and reciprocal transfer of cholesterol from HDL and LDL onto CM and VLDL (Deckelbaum *et al.* 1984; Hopkins & Barter, 1986). The subsequent action of hepatic lipase (EC 3.1.1.3) on triacylglycerol-rich HDL and LDL results in the formation of small dense HDL and LDL particles (Watson *et al.* 1994). A higher fractional catabolic rate of small dense HDL (Brinton *et al.* 1994) will result in lower HDL concentrations, a lipid profile consistently linked with increased risk of CHD. Of more recent origin are data which demonstrate a positive relationship between a preponderance of small dense LDL and increased risk of MI (Austin *et al.* 1988; Griffin *et al.* 1994). Thus, low HDL and increased prevalence of small dense LDL are suggested to be the atherogenic consequences of insulin resistance and central obesity (Reaven *et al.* 1993; Selby *et al.* 1993) arising from adverse effects of the latter on pathways of triacylglycerol metabolism.

#### SERUM LIPID PROFILES AND BODY FAT DISTRIBUTION IN WOMEN

The most notable distinguishing feature of the female lipid profile is the higher concentration of HDL-cholesterol (Fig. 4; Gregory *et al.* 1990) which almost certainly provides significant protection against premature CHD. Although LDL-cholesterol

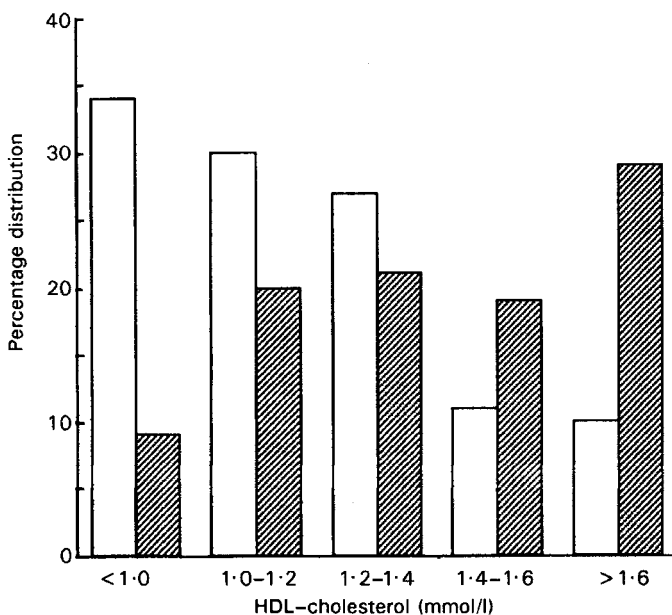


Fig. 4. Percentage distribution of HDL-cholesterol by sex. (□) Men; (▨), women. (Redrawn from Gregory *et al.* 1990.)

concentrations increase following the menopause, adverse reductions in HDL are not so marked (Stevenson *et al.* 1993), and may help to explain why protective effects of female hormones extend for some period of time beyond the menopause. Lower fasting and postprandial concentrations of triacylglycerol are another notable feature of the female lipid profile, which through attenuation of the mechanism described previously may also offer significant protection against CHD. Young female subjects have triacylglycerol concentrations approximately 40% lower than their male counterparts and although triacylglycerol concentrations increase after the post-menopause, they do not reach levels found in older males and are generally close to values seen in young normolipidaemic males (Cohn *et al.* 1988). The ability to quantify LDL subtypes separated by their different densities has allowed comparisons of LDL subtype distributions (LDL I, LDL II and LDL III) in male and female populations. In young normo-lipidaemic subjects with normal body weight, there is a clear gender difference in LDL sub-type distribution, with females possessing more of the large buoyant LDL subtype (LDL I) and males more of the small dense LDL subtype (LDL III; Griffin *et al.* 1990; Tan *et al.* 1995), the reputedly atherogenic sub-type profile (Austin *et al.* 1990). Women and men are clearly distinguished by their different fat distributions, with greater preponderance of body fat located around the gluteal regions and less deposited centrally in women compared with men. With age there is a greater tendency for women to develop an androgenic fat distribution, although there remain clear distinctions between men and women (Ley *et al.* 1992). The recent demonstration by Cefalu *et al.* (1995), that variations in abdominal fat distribution account for 51% of the variation in insulin sensitivity in a large group of normal men and women provides support for the view that differences in body fat distribution may be the primary locus through which gender-related differences in CHD risk operate. However, beneficial effects of oestrogen on specific pathways of lipoprotein metabolism almost certainly add to

this protective effect of body fat distribution. These effects include: up-regulation of the LDL receptor and inhibition of hepatic lipase (McNamara *et al.* 1987; Tan *et al.* 1995) and increased synthesis of apolipoprotein A1, the transport protein of HDL.

#### ABNORMALITIES IN METABOLIC RISK FACTORS IN WOMEN

The proposal that women have a lesser susceptibility to CHD due to biological protection against development of metabolic risk factors is supported by the observation that when abnormal values of these risk factors are present they greatly reduce differences in CHD risk between men and women. This is clearly seen in women with non-insulin-dependent diabetes mellitus (NIDDM) in whom risk of CHD is increased 4–5-fold, whereas in men, NIDDM increases risk of CHD by only 2–3-fold (Barrett-Connor *et al.* 1991). Another example is afforded by that of Asian women living in the UK, but born in the Indian sub-continent, who have a very high prevalence of insulin resistance and central obesity and in whom risk of CHD is rising faster than in the male Asian population (Balarajan, 1991).

Studies of normal non-diabetic female populations also support the proposal that abnormalities in metabolic risk factors are important determinants of CHD in women. A number of studies indicate that these markers may be more important in distinguishing risk of CHD in females than the established risk markers which have been derived from studies of male populations. This is best illustrated by consideration of findings from studies which have evaluated the impact of serum triacylglycerols and central obesity on CHD risk in women. Although fasting triacylglycerols have not been shown to be independent markers of risk for CHD in studies of male populations, at least four prospective studies of female populations have demonstrated elevated fasting triacylglycerol values to be strongly associated with CHD risk (Kannel *et al.* 1971; Bottinger & Carlson, 1982; Johanssen *et al.* 1988; Bengtsson *et al.* 1993). The Framingham study showed that in women the strongest predictors of CHD risk were a triacylglycerol value greater than 1.7 mmol/l and HDL value less than 1.3 mmol/l (Castelli *et al.* 1986; Castelli, 1988). A prospective follow-up of 1462 women over a 20-year period in Gothenburg, Sweden (Bengtsson *et al.* 1993), demonstrated a strong association between serum triacylglycerol concentrations and CHD mortality. Although total blood cholesterol and BMI were initially shown to be significantly associated with CHD in this population, correction for effects of elevated triacylglycerol in the former and central obesity (waist:hip ratio; WHR) in the latter, removed any significant effects of these two variables. A number of studies have shown central obesity to be a strong risk factor both in men and women, although studies in women (Lapidus *et al.* 1984; Higgins *et al.* 1988; Bengtsson *et al.* 1993; Manson *et al.* 1995) generally produce values for relative risks which are higher than those found in men (Larsson *et al.* 1984; Ducimetiere *et al.* 1986; Donahue *et al.* 1987). One of the most recently reported studies of anthropometric variables and risk of CHD in women was the 18-year follow-up of the Nurses Health Study (Manson *et al.* 1995). This study showed BMI, WHR and weight gain in adult life, to be significant risk factors in CHD. Although WHR was not as strong a predictor of total mortality as BMI, the WHR was a very strong predictor of death due to CHD, suggesting that this marker is a specific and highly discriminating risk factor for this disease. The data from this study are of particular value because effects of smoking were controlled for and subjects who died within the first 4 years of follow-up were excluded from the analysis.

Some evidence which mitigates against insulin resistance as a particularly important risk factor for CHD in women is suggested by two studies which have shown no relationship between insulin sensitivity and CHD in women, but increased risk with

decreased sensitivity in men (Cullen *et al.* 1983; Modan *et al.* 1991). Questions regarding the central role of elevated triacylglycerols and the LDL III subtype as important risk factors in female CHD are also raised by the observation that hormone-replacement therapy, which is now generally accepted as having protective effects against CHD, results in significant increases in fasting triacylglycerol concentrations (Writing Group for the PEPI Trial, 1995) and in an alteration of the LDL subtype pattern towards the more atherogenic form (Griffin *et al.* 1993). These somewhat paradoxical findings may be explained by the possibility that the most important consideration is the prevailing concentration of HDL. When HDL levels are high, other risk factors become quantitatively less important; since HDL is consistently raised by HRT this may offer some explanation for these observations (Seed & Crook, 1994).

#### CONCLUSION

Women have a lower risk of CHD despite higher prevalence of established risk factors, particularly blood cholesterol and obesity. This may be due to their lower susceptibility to the 'metabolic syndrome' arising from the female pattern of body fat distribution, although this effect is almost certainly added to by the protective effects of oestrogen on specific pathways of lipoprotein metabolism. Raised serum triacylglycerols, lowered HDL and central obesity have emerged as strong discriminators of CHD risk in women and may be more valuable in identifying high-risk female groups than some of the established risk factors. Interventions based around these risk factors, i.e. mechanisms for reducing raised fasting and postprandial triacylglycerols and for preventing weight gain in middle life, may be more appropriate than those which have been used hitherto.

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