

Confounding and indication for treatment in evaluation of drug treatment for hypertension

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In research on the effectiveness of treatments, the randomised controlled trial is considered the best study design because it enables several sources of bias to be removed from the observation. The most important advantage of such a trial is that the baseline prognoses of patient groups are comparable so that unbiased estimates of the effects of a particular intervention can be obtained. In non-experimental (observational) studies allocation to drug treatment is, by definition, not random. This usually means that the prognoses of the patient groups are not comparable and any inferences drawn about the relative effects of treatment are therefore invalid.^{1,2} In studies of patients who are not randomly allocated to a treatment arm but receive treatment when their doctor decides to prescribe it, the onus is on the investigator to achieve comparability. We discuss the pitfalls of non-randomised comparisons of treatment effects. The results of a recently published study which suggested that hypertension should not be lowered too far by treatment and the subsequent debate provide an example of problems that may arise in validating the conclusions of such studies.

Confounding by indication

A sensible doctor prescribes drugs only to patients who need them—those who have indications that this treatment is required. Moreover, he or she will give priority to treating the most needy patients. When two patients seem to have indications but only one is being treated, the treated patient probably has more compelling indications than the second. The prognosis in any given group of treated patients will be different from that in untreated subjects because the latter will not generally have any indications for treatment. Furthermore, although many drugs can affect the course of a disease positively, the outcome in people with that disease compared with those who do not have it or have a less severe form may be worse or, at best, similar. At first glance, therefore, the evidence seems to show that the drugs induce the disease rather than curing it. This biased observation is considered to arise from confounding by indication.³

Non-randomised comparisons

Confounding by indication commonly creates unsurmountable problems for non-randomised research on treatment effects. Valid inferences can be drawn only

Summary points

Confounding by indications for treatment is a serious threat to the validity of non-randomised comparisons of treatment effects

Conclusions about the efficacy of treatment should not be drawn from comparisons of treated and untreated patients

Under some circumstances, confounding by indication in a non-randomised study can be limited or even removed in the design phase or data analysis

Reported increased risks of heart disease in hypertensive patients with low blood pressure during treatment may be attributable to pre-existing severe atherosclerosis rather than “overtreatment”

Unequivocal rejection of all non-randomised studies assessing treatment effects is unjustified

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under those rare circumstances in which (a) groups of patients with the same indications but different



Can blood pressure be lowered too far? The debate continues

Confounded comparisons

- “Do not accept chemotherapy because you will die of cancer”
- “Refuse to take non-steroidal anti-inflammatory drugs because people who don’t use them have less arthritis”
- “Avoid antihypertensive treatment as those who are treated have higher stroke rates”

The indications for drug use, because of their natural association with prognosis, may confound comparison so that it looks as if the treatment causes the disease

treatment can be compared and (b) residual dissimilarities in characteristics in patients receiving different drugs for the same indications can be adjusted for. For example, Psaty et al compared the effects of several antihypertensive drugs on the risk of angina and myocardial infarction. They used a case-control study design, and took ample measures to exclude confounding by indication.⁴ An alternative approach would be to include only those subjects who are similar for all prognostic factors (such as a history of disease or presence of other risk factors) except treatment.

Research on the risks associated with drugs also gives examples of study designs in which a shared indication, combined with adjustment for any remaining prognostic discrepancies, limits confounding by indication. The putative association between non-potassium sparing diuretic drugs and sudden cardiac death in treated patients with hypertension was recently examined in two case-control studies. These compared the risks of sudden death in patients taking different classes of antihypertensive drugs, especially diuretic drugs.⁵ These examples are exceptions to the rule that non-randomised comparisons of treatment effects should not be trusted. That rule applies particularly when treated patients are compared with untreated ones rather than with patients treated with different drugs for similar indications. However, even when several confounding factors are taken into account, the validity of findings on drug benefits and risks in non-randomised studies may be questionable. This is illustrated by the debate that followed the publication of a recent case-control study on the putative risks of calcium antagonist drugs in the treatment of hypertension.^{6,8}

In theory, the effect of confounding by indication could be completely removed by measuring all the patient characteristics which the doctor considered formed the basis of the indications for treatment and adjusting for these subsequently in the statistical analysis. Table 1 gives an example of adjustment for confounding by indication in a non-randomised study

Table 1 Crude and adjusted rate ratios for death from cardiovascular causes in untreated and drug treated hypertensive women

| | Rate ratio (95% CI) |
|--------------------------------|---------------------|
| Crude value | 1.0 (0.6 to 1.5) |
| Adjusted for: | |
| Age | 0.7 (0.4 to 1.1) |
| +Body mass index, pulse rate | 0.6 (0.4 to 1.0) |
| +Smoking, lipid concentrations | 0.6 (0.4 to 0.9) |
| +Diabetes | 0.5 (0.3 to 0.9) |

which compared the effectiveness of drug treatments for hypertension over 10 years of follow up in the Netherlands. Here, as a first approach to reducing confounding by indication, a comparison was made between treated and untreated hypertensive subjects rather than between treated hypertensive subjects and the rest of the population.⁹ Adjustment for differences in patient characteristics that were relevant to the prognosis caused a striking change in the risk estimates (table 1).

For statistical adjustment to be useful, several requirements must be met. Firstly, all relevant determinants of the indications should be known. Secondly, the information on confounding factors should be of sufficient quality (precision) to allow complete adjustment. Finally, the number of patients in the study should be sufficient to allow for statistical modelling of many confounding variables. If only some variables that determine the indication for treatment are available, statistical adjustment will be incomplete. In the example of hypertension shown in table 1, information on confounding by indication is clearly incomplete. A family history of hypertension, for example, could affect the doctor’s decision to start treating a patient. Consequently, the rate ratio of disease in treated versus untreated hypertensive patients may still be biased upwards.

Blood pressure should not be lowered too far

Recently, Merlo et al presented an analysis from the study of men born in 1914.¹⁰ This showed that those patients treated for hypertension who had a diastolic blood pressure below 90 mm Hg during treatment were at a greater risk of myocardial infarction than the remainder of the population.¹⁰ An almost fourfold increase in risk was estimated, even after adjustment for several confounding variables. The authors concluded that blood pressure during treatment should not be reduced below 90 mm Hg.

This conclusion is surprising for several reasons. Since the authors estimated as 1.1 the risk of myocardial infarction in treated hypertensive patients whose blood pressure was greater than 90 mm Hg compared with untreated hypertensive patients, they ought to have concluded that hypertensive patients should not be treated at all. More importantly, the validity of their conclusion in the patients who had lower blood pressures during treatment is highly questionable.

Firstly, since valid measurement of all factors that influence a doctor in prescribing a drug seems impossible, part of the observed increased risk is attributable to residual confounding in relation to indication. This is well illustrated by the 90% increased risk in treated hypertensive patients compared with the rest of the population after extensive adjustment for confounding variables. These variables included previous myocardial infarction, previous cerebrovascular disease, ischaemic heart disease, intermittent claudication, diabetes mellitus, raised systolic blood pressure, duration of hypertension, hypercholesterolaemia, hypertriglyceridaemia, raised serum creatinine con-

centration, obesity, use of cardiac glycosides, and a history of smoking.

Secondly, a comparison of the risk of ischaemic heart disease events in treated patients with a low blood pressure and treated patients with a high blood pressure, which is therefore conditional on treatment, would be more relevant and valid. The results of this analysis using the data provided by Merlo et al are shown in table 2. These show that the presumed increased risk in treated patients with lower blood pressure compared with those with higher blood pressure is far from statistically significant.

Whether and why a low treated blood pressure puts a patient at risk of myocardial infarction is important. Several studies have suggested that the association between diastolic blood pressure levels and risk is J shaped.¹¹⁻²⁰ One suggests that a low diastolic blood pressure compromises coronary blood flow and subsequently increases the risk of coronary heart disease.²¹ Results from several studies of hypertensive middle aged people have shown that the use of medication and the reduction in blood pressure after treatment may contribute to the J shaped association.^{16 17 19 22 23} These findings have caused heated debate on the diastolic blood pressure that should be achieved with antihypertensive treatment.²³⁻²⁵ Strong evidence against an important contribution of antihypertensive treatment comes from the observation that the J shaped association is also found in control groups in trials of drugs for hypertension.^{5 6 22} In the systolic hypertension in the elderly program trial in older people with isolated systolic hypertension, the mean diastolic blood pressure was lowered from 77 mm Hg to 68 mm Hg and the number of deaths from cardiac causes was not increased but reduced.²⁶ Moreover, in observational studies a J shaped association between diastolic blood pressure and cardiovascular risk was also reported in patients who were not taking antihypertensive drugs.^{13 25}

Sleight proposed that stiffening of the large arteries in elderly people might lead to high systolic and low diastolic blood pressures, and that stiffer arteries are associated with an increased risk of coronary heart disease.²⁷ Widespread atherosclerosis may be the link between stiffening of large arteries, low diastolic blood pressure, and an increased risk of cardiovascular disease.^{28 29} In support of this view, Witteman et al reported a J shaped association between the fall in diastolic blood pressure and the progression of atherosclerosis of the abdominal aorta in postmenopausal women.³⁰ The results indicated that a fall in diastolic blood pressure may indeed be a result of stiffening of the vessel wall, as indicated by the progression of aortic atherosclerosis. Recent findings of thicker carotid artery walls in subjects with low untreated diastolic blood pressure who were participating in the Rotterdam study confirmed this.³¹

Conclusion

In studies on the effects of treatment, non-randomised comparisons can be affected by confounding by indication, and this may result in wrong conclusions. Appropriate methods of limiting confounding exist, however, and this means that non-experimental studies assessing treatment effects should not be rejected

Table 2 Incidence of ischaemic cardiac events in relation to diastolic blood pressure in elderly men being treated for hypertension¹⁰

| Diastolic blood pressure | No of events | Person years | Incidence rates (per 1000 per year) | Rate ratio (95% CI) |
|--------------------------|--------------|--------------|-------------------------------------|---------------------|
| ≤90 mm Hg | 13 | 212 | 61 | 1.70 (0.78 to 3.60) |
| >90 mm Hg | 20 | 556 | 35 | |

unequivocally. Nevertheless their conclusions should not be accepted uncritically,³² particularly when comparisons between treated and untreated patients are made, as in the report of Merlo et al.¹⁰ The conclusions of Merlo et al may compromise the quality of care currently given to many hypertensive patients as they may lead to stopping antihypertensive treatment and consequently to stroke or myocardial infarction.¹⁰ Before any change in the current goals of blood pressure treatment is made, unequivocal evidence must be provided that the observed association between low diastolic blood pressure and the risk of myocardial infarction is not an artefact resulting from pre-existing severe atherosclerosis. Randomised trials are under way to clarify this issue.³³ In the meantime, there is no reason to deny the fact that treated hypertensive patients still have a high incidence of stroke and heart attacks. That, after all, is the reason for treating them in the first place.

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Women's health

Women's health is a global issue

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This is the first of three articles explaining the impact of women's health on the international community

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All over the world, women live longer than men.¹ The largest differences are in eastern Europe, the Baltic states, and central Asia. In the Russian Federation women live 12 years longer than men; in most developing countries the differences are smaller, with women outliving men by only 3 years in Africa.

In developing countries, life expectancy for both sexes has increased from 40 to 63 years since 1960, and in countries with high incomes it is now at least 75 years.² Only in Uganda and Zambia has life expectancy dropped—from 48 to 43 for women and from 46 to 43 for men—due to the impact of AIDS.¹

Although women are living longer, they do not necessarily live better, healthier lives. In developing countries, communicable diseases, together with illnesses relating to childbirth, account for most morbidity in women (fig 1). In the developed world too, women are sicker than men, according to their own assessments of their physical and psychological well-being.³

Lesley Doyal, professor of health and social care at the University of Bristol, explains that "While women risk contracting the same endemic diseases as men, both biological and social factors may increase exposure or worsen the effects."³

Global influences on women's health

Some things affect women more often than men, regardless of where they live. These include poverty, changing demography (birth rates and an aging population), gender, violence against women, and lack of research about women.

Poverty

Over 70% of the 1.3 billion people living in poverty are women.⁴ The link between poverty and ill health is well established.⁵ The social causation hypothesis relates health to structural factors such as working environment or behavioural factors such as diet.⁶ To reduce poverty and therefore improve health, the World Bank

Summary points

Although women live longer than men, they are less healthy

Because of the strong preference for male children in many parts of the world, women receive inferior nutrition and healthcare from birth

Poverty, discrimination, and violence have a great adverse effect on women's health

Projects which aim to reduce gender inequalities are focusing on educating and empowering women by encouraging both sexes to challenge gender stereotypes

has encouraged governments to invest in policies which support economic opportunities for women.¹

Changing demography

The total birth rate has fallen by 40% in the past 30 years and the percentage of contraceptive users has increased from around 14% in 1960-5 to an estimated 57% of women of reproductive age in 1994.⁷ Where there is a choice, women delay childbirth. Research in Britain has shown that at least one woman in five now in their 20s and 30s will have no children.⁸ The feminist writer Joan Smith notes that "in the past, without reliable methods of contraception, women had little choice. For centuries, people mixed up the fact that nearly all women had children with the assumption that they all passionately wanted to do it. Take away the element of biological inevitability and what happens? A substantial minority turn out to have other things on their mind, whether it's a career or a life based around lovers and close friends."⁹

Research by the Special Programme of Research, Development and Research Training in Human Reproduction based at the World Health Organisation shows that millions of women say that they want no more children in the near future or have reached their desired family size, but these women are not using any contraception. This may be due to lack of access to family planning services or because healthcare planners have not taken into account women's needs and perspectives.

The proportion of elderly people in the population is increasing worldwide. There are at least 302 million women in the world who are over the age of 60, in comparison to 247 million men. Because women live longer than men all over the world, the ratio of women to men over the age of 60 ranges from 109:100 in eastern and western Asia to 168:100 in eastern Europe.¹

Older women's health needs are different from those of men, particularly as many of these elderly women will have experienced poor nutrition and reproductive ill health. Because women tend to marry older men, many of these women will be widows, and this increases the risk of poverty, ill health, and isolation.

Gender

Gender describes those characteristics of men and women which are socially constructed, in contrast to sex, which is biologically determined. As Rebecca Cook, professor in law and medicine at the University of Toronto, explains: "Leadership through success in battle is male gendered, whereas caring for the dependent young, sick, and elderly is female gendered. It is obvious that women can be political and industrial leaders, and that men can be caregivers, but it has been considered exceptional for people to assume a gender role at variance with their sex."¹⁰

For women, gender differences may mean inequality and discrimination. "Not all women are worse off than men," says Professor Lesley Doyal, "but in most societies the male is valued more highly than the female."³

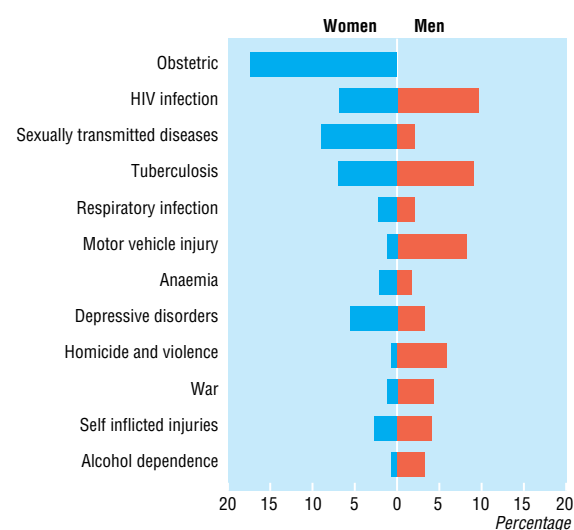


Fig 1 Burden of disease in adult men and women aged 15-44 years in the developing world, 1990. Adapted from *World Development Report 1993*, p28²



Fig 2 Brick making generates income for women in Uganda

Violence against women

The 1993 World Development Report estimates that 5-16% of the healthy years of life lost to women of reproductive age can be linked to victimisation based on gender, rape, and domestic violence.² Women refugees are at particular risk of sexual abuse and violence—the refugee population has grown from 2.5 million in 1970 to over 18 million in 1995.¹¹

There is not much reliable, population based data but it is clear that violence can result in long term mental, physical, and sexual health problems.¹² Most violence is directed at women and most perpetrators are men, often known to the women. Violence against women by their partners cuts across socioeconomic, religious, and ethnic lines.¹³

Lack of research about women

Research on populations tends to be undifferentiated by sex and has excluded proper studies of women.¹⁴⁻¹⁶ The grounds for excluding women are that the menstrual cycle introduces a potentially confounding variable in analysis of data that can be overcome only by larger subject pools and more complex data gathering and analysis. A further protective reason has been that experimental use of treatments might expose fetuses to unknown risk, and excluding women who might be pregnant involves intrusive questioning or testing.¹⁷

Bernadine Healy from the National Institutes of Health in the United States summarises the task: "It is now time for a general awakening—women have unique medical problems."¹⁸ Some diseases are unique to women; others, such as coronary heart disease, may have different effects in women.

Health of women in the developing world

Issues affecting women in the developing world may also be applied to women living in socioeconomically deprived areas in the developed world. Important among these are education, lack of autonomy, legal status, preference for sons, traditional practices, lack of access to health care, work and environmental health hazards, and unequal human rights.

The Girl Child Project²⁰

The Girl Child Project was established by the Family Planning Association of Pakistan to raise awareness among young girls and their families of unfair and unnecessary discrimination against girls.

“People here don’t educate their girls because to them girls are not theirs,” points out 16 year old Nacema Ansari from Ratta Amral, Rawalpindi. “Girls are seen as belonging to their future in-laws’ families and any investment in their future is futile. They go to their husbands’ homes at a young age, usually anywhere from 13 to 17. The rest of their lives are spent looking after in-laws, and bearing and bringing up children to prolong and strengthen their husband’s family line.”

In the project girls are given information on health, hygiene, nutrition, education, first aid, food preservation, and women’s rights. Girls have been taught how to conduct adult literacy training, grow trees, and promote environmental cleanliness.

Shabnam Naheed, 16, who lives in Baldia, said, “In my own family, my mother used to give meat to my brothers first and then to us girls. I learnt during the workshops that this was not right. So I went home and told my mother that even the Prophet Muhammad had said to treat girls equally. Now we all eat well.”

Education

Globally, more than 960 million adults are illiterate, two thirds of whom are women.¹⁹ Households with more education enjoy better health, both for adults and for children.¹ Women with even a few years of schooling have more self confidence; they assume responsibility, communicate more with their husbands, and may have a higher status in the family, giving them more say in health decisions.²

Lack of autonomy

Women can know how to care for minor illnesses and recognise serious illness but can lack the autonomy to decide when to go for treatment for themselves or for a child. For example, well informed women in India find it hard to take their own decisions about family planning, as Dr Sundari Ravindran from the Centre for Development Studies in India describes: “When husbands disapprove of their wives practising contra-

ception, it is an exceptionally brave woman who defies the authority of their husband.”¹³

Legal status

Laws and customs about land ownership, inheritance, marriage, or divorce in many countries discriminate against women, often contributing to their poverty and poor health. For instance, in Lesotho only widows and women who are legally determined to be household heads may apply for credit in their name. Wives, even if they are de facto heads of households, are barred from applying for credit.²¹ In Kenya, rights to inherit from their fathers belong only to sons.⁸

Preference for sons

In regions where sons are highly valued, girls may be given inferior nutrition and health care from birth and weaned early to allow the mother to conceive a boy as soon as possible.²² In extreme cases this preference may lead to prenatal sex selection in favour of boys, or to infanticide.¹¹

Traditional practices

Traditional practices such as female genital mutilation may harm women, and dowry and bride price may lead to physical abuse, intimidation, or even death. Many cultures place high value on having children at a young age, perhaps even before girls have reached physical maturity. In Nepal, one third of girls are married by the age of 15²³; in India, southeast Asia, and subSaharan Africa, one third to one half are married during adolescent years, typically to men a decade older.

Lack of access to health care

In the developing world, women use health services less than men.¹¹ This may be because facilities do not exist or because the costs of services are prohibitive. Often health services are insensitive to the cultural needs of women: in many Middle Eastern countries, for example, most doctors are men, despite a strong belief that women should not be seen after puberty by men who are not relatives.²

In some places, services are narrowly centred around women in their reproductive roles.¹⁵ Individual health services such as prenatal care and immunisations may be offered on different days, meaning that women have repeatedly to return with their children.

Work and environmental health hazards

Outside the home, women tend to work in the informal sector or in smaller, less regulated enterprises than men. Poor conditions predispose these women to health risks ranging from exposure to carcinogenic chemicals or excessive noise, heat, and humidity, to physical strain, eye strain, and allergic reactions.¹¹

In the home, in most cultures women are responsible for maintaining the household, including caring for children and elderly and sick people. Every day a woman may need to walk up to 10 kilometres for water or fuel, carrying loads of 20 kg or more on her head.¹¹

Unequal human rights

Women in many societies have little or no access to education and may be subject to laws, practices, stereotypes, and prejudices that are harmful to them. As human rights lawyer Rebecca Cook notes, “The



DOMINIC SANSONI/PANOS

Fig 3 There is a trend towards educating and empowering women—classroom in Brunei

Inalienable human rights

The human rights of women and of the girl-child are an inalienable, integral, and indivisible part of universal human rights. The full and equal participation of women in political, civil, economic, social, and cultural life, at the national, regional and international levels, and the eradication of all forms of discrimination on grounds of sex are priority objectives of the international community.—Vienna Declaration and Programme of Action adopted by the World Conference on Human Rights, Vienna, 25 June 1993

poor state of women's health in many regions of the world, including within deprived socioeconomic populations in developed countries, can be seen as one result of women's inability to protect their own interests.⁹ 10

Health of women in the developed world

Many women, particularly in the developed world, are challenging the traditional view that a woman's place is in the home, but in western Europe women are still outnumbered by men in higher education (93 women per 100 men).¹ This is in spite of the fact that in the developed regions outside western Europe, in Latin America and the Caribbean, and in western Asia, the population has more women than men.¹ At the end of 1994, 10 women headed governments, and the number of countries with no women ministers fell from 93 to 59 between 1987 and 1994.¹ Women rarely represent more than 1-2% of senior management positions in business.¹

Changes in central and eastern Europe and the former USSR have had an adverse effect on health. Maternal and infant mortality have risen, and morbidity from circulatory diseases in women has increased. Women have more mental health problems and there

is more violence against women, often linked with alcohol intake by men.

In areas where the birth rate has fallen women are less exposed to the hazards of childbearing. The rapid changes in women's economic roles, however, may raise issues about how women are to cope with their dual roles and increased workload.

Conclusion

As far back as the first general assembly of the United Nations in 1945, female delegates demanded special attention for women's issues. During the United Nations Decade for Women (1976-85) many organisations began to appreciate the link between women's status, fecundity, and development and started implementing small scale community projects for women's development. Many of these addressed the need for income generation and new skills. There is now a trend towards educating and empowering women and encouraging women to get involved in developing strategies for change. Projects also aim to encourage both women and men to challenge gender stereotypes.

Many employers continue to underinvest in women. The World Bank believes that markets fail to capture the benefit to society of investing in women and girls. It argues that public policy can reduce gender inequalities—for example, by modifying laws to ensure equal opportunities. It recommends that governments should redirect public money to investments offering the highest social returns and target those interventions which correct for gender inequalities.²

Provision of public handpumps in Imo State, Nigeria, reduced the median time that each household spent on water collection in the dry season from six hours a day to 45 minutes.²



Fig 4 Women's economic roles have changed rapidly, but traditional practices carry on—spinning wool in Ethiopia

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