

# Similarities in the epidemiology of neural tube defects and coronary heart disease: is homocysteine the missing link?

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## Abstract

**It is hypothesised that a single aetiological pathway could explain both the strong ecological association between the birth prevalence of neural tube defects (NTD) and coronary heart disease (CHD) mortality and the potential efficacy of dietary measures, especially increased folic acid intake, in their prevention. The epidemiological similarities between NTD and CHD are strong and consistent suggesting that the relation is real rather than artefactual. It is suggested that this epidemiological association reflects a shared aetiology arising from the role of disturbed homocysteine metabolism in the pathogenesis of both conditions. Current public health measures designed to increase the intake of periconceptual folic acid in women, reinforced by a broadening of this policy to target both sexes throughout life, will (if successful) result in a reduction in both the birth prevalence of NTD and the incidence of CHD, although not necessarily contemporaneously. If disordered homocysteine metabolism is the cause of both NTD and CHD, this has implications for future research and preventive strategies for these serious and often lethal diseases.**

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There has been much interest in the possible fetal and infant origins of adult cardiovascular disease (CVD).<sup>1</sup> Evidence has accumulated that moderately increased levels of homocysteine are also a risk factor for CVD.<sup>2</sup> In this paper, we review the evidence for a possible aetiological connection between two apparently unrelated diseases of infancy and adult life: neural tube defects (NTD) and coronary heart disease (CHD). We propose that a biologically plausible single aetiological pathway could explain the strong ecological correlation between the two disorders. The hypothesis revolves around the role of homocysteine in human metabolism and how it may be influenced by both genetic and dietary factors.<sup>3</sup> This paper will examine the epidemiological similarities of the two diseases, discuss the possible role of homocysteine as a common causal agent and assess the implications of the hypothesis.

## Epidemiological similarities between NTD and CHD

There are several epidemiological similarities between NTD and CHD. There is marked

geographical variation in the prevalence of NTD.<sup>4</sup> Britain and Ireland have long been regarded as having the highest risk in Europe if not the world.<sup>5</sup> Within the British Isles, NTD displays a familiar pattern of increasing prevalence from south east to north west.<sup>6,7</sup> An analysis of data from the British Perinatal Survey of 1958<sup>7</sup> demonstrated that this regional trend was independent of social class, a variable that has repeatedly been shown to be associated with NTD variation.

A remarkably similar geographical pattern of CHD mortality has been observed.<sup>8,9</sup> Stocks<sup>10</sup> drew attention to the high correlation between prenatal plus infant mortality rates from NTD and female cardiovascular mortality in England and Wales. He hypothesised a common aetiological factor, possibly water hardness, to account for the phenomenon. And, as with NTD, the risk of CHD is higher in the British Isles than in the rest of Europe.<sup>11</sup> The exception is Finland, which has a high risk of CHD but a low risk of NTD. Disease patterns in Finland may be difficult to interpret; for example, there are around 30 rare recessive diseases that are commoner than in other populations.<sup>12</sup> While the high rates of CHD are likely to be attributable in part to well described risk factors, at present there is no clear explanation for the low NTD prevalence.

While fluctuating secular trends in NTD prevalence have been described in many areas, the steady recent decline in Britain seems to have begun in the 1970s<sup>13-15</sup> and has continued since then.<sup>16,17</sup> Around a decade after the prevalence of NTD began to decline, a similar fall in mortality from CHD was reported<sup>18</sup> (fig 1). This occurred in all age groups suggesting a strong period of death rather than cohort effect.<sup>19</sup> A parallelism between NTD prevalence and CHD mortality is also apparent in the United States where both peaked and then started to decline about a decade earlier than in Britain.<sup>4,20</sup>

There is also a remarkable similarity in the socioeconomic distribution of the two diseases. Reliable data are available up to the mid-1970s and demonstrate a higher prevalence of NTD in populations of low socioeconomic position in several countries including Britain,<sup>21,22</sup> Australia,<sup>23</sup> Finland<sup>24</sup> and the USA.<sup>25</sup> Thus a higher rate in poorer communities was found irrespective of the relative frequency of the disease. Few recent studies have investigated the relation between socioeconomic position and NTD prevalence perhaps in part because of the decline in the prevalence of NTD and the

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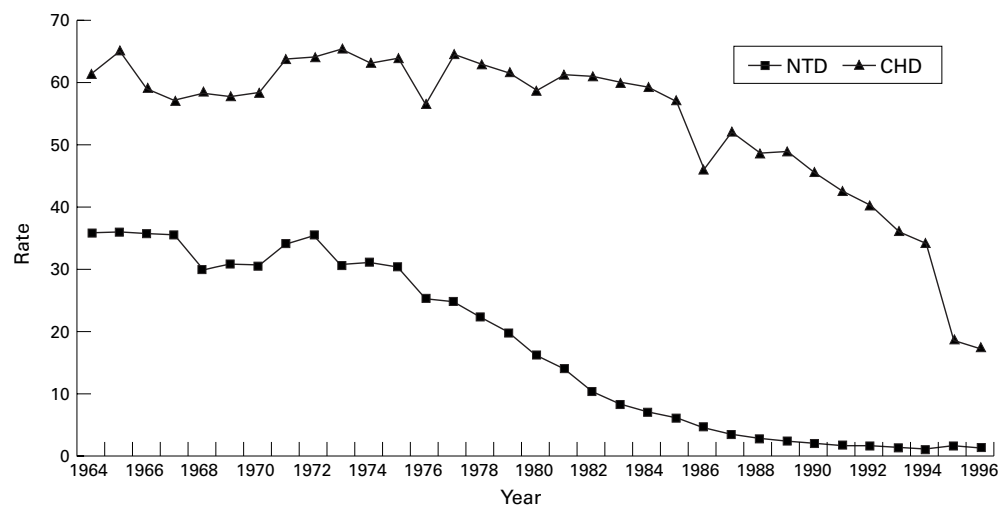


Figure 1 Secular trends in NTD birth prevalence (per 10 000) and CHD mortality (women, 25–64 years, per 100 000) 1964–96. Source: Office for National Statistics (formerly Office of Population Censuses and Surveys).

growing use of prenatal diagnosis and therapeutic abortion. Nevertheless, the inverse association between NTD prevalence and socioeconomic position seems to have persisted in England and Wales<sup>26</sup> and in Newfoundland, Canada (where NTD prevalence has not declined).<sup>27</sup>

In the case of CHD, mortality in men in social class I was double that of the lowest two classes in England and Wales in the 1950s<sup>8</sup> whereas since the 1960s, CHD mortality both sexes has been consistently reported to be higher in the lower socioeconomic groups.<sup>28</sup> This apparent social class crossover should be regarded with caution as there is some evidence that the earlier reported association of high CHD mortality with high socioeconomic position may have been artefactual.<sup>29–30</sup>

#### A common aetiological relation—disturbed homocysteine metabolism

Recent advances in the understanding of cellular pathophysiology suggest that homocysteine might be the “missing link” between NTD and CHD.

Homocysteine, folate and vitamins B6 and B12 participate in several interrelated metabolic pathways, many of which are necessary for cell replication,<sup>31</sup> as shown in figure 2. Removal of a methyl group from methionine produces homocysteine. This potentially toxic compound may either be irreversibly degraded to cysteine by the enzyme cystathionine- $\beta$ -synthase or converted back to methionine by the enzyme methionine synthase thereby conserving methionine. This latter reaction is dependent on the presence of both vitamin B12 (in the form of methylcobalamin) and a metabolite of folic acid (5-methyl tetrahydrofolate). The production of this folate derivative is in turn driven by another enzyme, methylene tetrahydrofolate reductase (MTHFR).

Homocysteinaemia has been shown to be associated with folate depletion<sup>32</sup> but the causal direction is unclear. Folate deficiency may impair the conversion of homocysteine to cysteine leading to excessive and potentially toxic blood homocysteine levels. Alternatively,

folate might become depleted as a consequence rather than a cause of impaired homocysteine metabolism. In either event, it appears that interruption of the remethylation of homocysteine leads to a rise in both intracellular and plasma homocysteine levels, impairing the production of S-adenosylmethionine (SAM), the ultimate methyl donor for DNA synthesis, adversely affecting cell replication. Increasing the intake of key nutrients such as folic acid<sup>33</sup> and possibly vitamins B6 and B12<sup>34</sup> may reverse this process.

Diet alone is unlikely to determine the efficiency or otherwise of homocysteine metabolism as several of these biochemical processes are also dependent on enzymatic activity that is partly genetically determined. While homozygous deficiencies of cystathionine synthase and MTHFR are rare, in 5–11% of the population a genetic mutation is associated with a variant of MTHFR that impairs enzyme activity.<sup>35</sup> Other gene defects that could impair homocysteine metabolism are those affecting methionine synthase and its cofactors derived from cobalamin metabolism.<sup>36</sup> However the relative contributions of nutritional and genetic factors remain uncertain.<sup>37–38</sup>

#### Neural tube defects and homocysteine

Early evidence for a possible role for homocysteine in the aetiology of NTD came from Thiersch who in 1952<sup>39</sup> described an apparently teratogenic effect of a folic acid antagonist, aminopterin. In 1964, Hibbard<sup>40</sup> postulated that folate deficiency could have an adverse effect during early embryogenesis, and supportive evidence was provided shortly thereafter by Hibbard and Smithells<sup>41</sup> who found that two thirds of mothers with NTD pregnancies had deranged folic acid metabolism.

The importance of folate in the aetiology and prevention of NTD is now widely accepted with several intervention studies<sup>42–45</sup> indicating that folic acid exerts a protective effect against both primary and recurrent NTD conception in mothers. Exactly how folate deficiency might interact with genetic vulnerability has not been

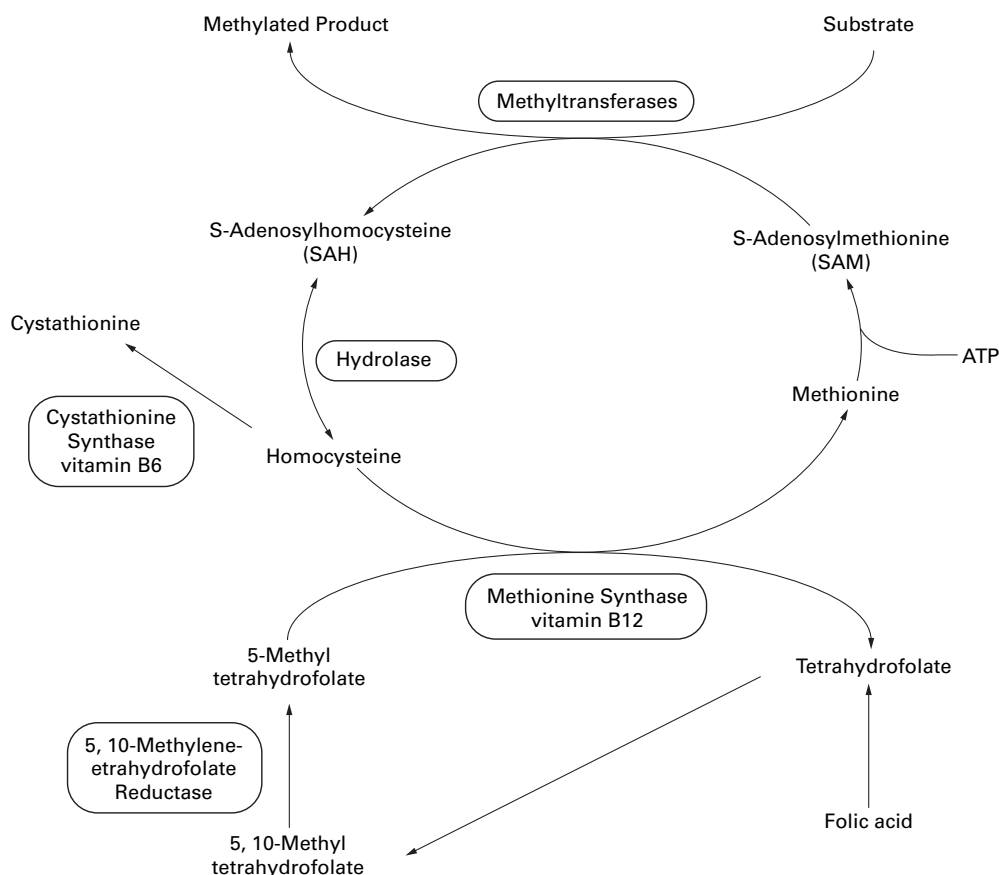


Figure 2 Homocysteine metabolism.

established. Homozygosity for MTHFR abnormality (that is, enzyme thermolability) has been shown to increase the risk of NTD<sup>33</sup> but whether the aetiologically relevant disturbance is in the maternal or fetal metabolism is uncertain. The mechanism whereby homocysteinaemia might cause NTD also remains unknown. An accumulation of homocysteine could be directly toxic to the developing fetal neural tube, which closes between 15 and 28 days post conception.<sup>46</sup> Alternatively, decreased methionine production would in turn reduce the availability of the methionine metabolite SAM, leading to disruption of normal neural crest formation at a time of rapid cell division.<sup>33</sup>

### Coronary heart disease and homocysteine

Direct evidence that folic acid deficiency plays a central part in the aetiology of CHD is unavailable. Numerous dietary factors have been studied, among them fruit and vegetables, the intake of which is inversely related to CHD risk in many observational epidemiological studies.<sup>47-49</sup> The dominant explanatory hypothesis invokes the antioxidant vitamins  $\beta$ -carotene,  $\alpha$ -tocopherol (vitamin E) and vitamin C.<sup>50</sup> However, randomised controlled trials of supplementation with these vitamins have been disappointing with respect to cardiovascular disease risk.<sup>51-53</sup> The cardioprotective factor in fruit and vegetables may turn out to be folate rather than antioxidant vitamins.

Whatever the precise aetiological mechanism, evidence is accumulating that increased

blood levels of homocysteine increase the risk of vascular disease. Studying an infant (interestingly of Irish descent) with homocystinuria, McCully<sup>54</sup> suggested that hyperhomocysteinaemia results in arteriosclerotic disease. Homocysteine may be toxic to the vascular endothelium either by disturbing smooth muscle function<sup>55</sup> or structure,<sup>56</sup> which could in turn accelerate atherogenesis. This could explain the marked association between increased plasma homocysteine levels and the risk of cardiovascular disease.<sup>57-59</sup>

More than 20 case-control and cross sectional studies have confirmed a positive relation between moderate hyperhomocysteinaemia and the risk of cardiovascular disease.<sup>60</sup> Because these moderate increases in homocysteine are too common to be attributable to the rare homozygosity for dysfunctional cystathionine synthase alleles, it has been postulated that they may be a result of another form of genetic susceptibility mediated through the production of the thermolabile variant of the enzyme MTHFR. Homozygosity for the variant MTHFR affects up to 11% of people in white populations<sup>61</sup> but three recent studies to determine whether these people had an increased risk of premature CHD<sup>62</sup> found no association.<sup>63-65</sup>

However, the role of dietary folate was not explored in these studies. Diet may be critical in both the minor and common genetic variants. A high intake of folic acid, possibly in conjunction with vitamins B6 and/or B12,<sup>34</sup>

may counter any increased risk by lowering plasma homocysteine levels thus increasing the availability of the substrate needed for the activity of MTHFR. The faulty genotype would therefore only become pathogenic when accompanied by marginal or low folic acid intake.<sup>58</sup> Indeed a Canadian retrospective study has shown that serum folate correlates inversely with the risk of fatal CHD.<sup>62</sup> More recently, a large American cohort has also reported lower relative risks for both fatal and non-fatal CHD for women with a higher intake of folate.<sup>66</sup> The logical next step is to initiate randomised controlled trials of folate supplementation to evaluate its impact on cardiovascular outcomes.<sup>67 68</sup>

### Hypothesised aetiological and epidemiological links between homocysteinaemia, NTD and CHD

We suggest that the epidemiological relation between NTD and CHD is real rather than artefactual. The relation exists because homocysteine occupies a pivotal position on the aetiological pathway to both NTD and CHD. In biological terms, an excess of homocysteine or one of its metabolites is potentially toxic to the human organism both in early intrauterine life, when it can disrupt the development of the fetal nervous system, and later in the life cycle, when it can damage the cardiovascular system.

Three supplementary hypotheses flow from the above. Firstly, mothers of children with NTD may be at increased risk of CHD. Secondly, because of varying susceptibility, homocysteine toxicity does not necessarily always manifest itself within individuals but is apparent at a population level, thereby explaining the ecological correlation between NTD and CHD. Thirdly, the pathogenic effects of homocysteinaemia may be partially or totally counteracted by increasing the intake (by dietary or other means) of key nutrients, especially folate and perhaps vitamins B6 and B12.

### Implications and future directions

Current public health measures designed to increase the intake of periconceptual folic acid in the population will, if successful, result in a reduction in the incidence of NTD. Several countries, including the US<sup>69</sup> and UK,<sup>70</sup> have issued official recommendations that all women planning pregnancy should receive extra folic acid before conception and during the first 12 weeks of pregnancy. The impact of this advice, either on dietary intake of folic acid or on the prevalence of NTD, seems to have been disappointing<sup>71 72</sup> and it is probable that the recommended doses are too small. According to the homocysteine hypothesis, a reduction in CHD incidence within two decades could be expected if folate supplementation were continued in this group.

Targeting this group of people alone may be inappropriate from both a behavioural and a public health perspective.<sup>73</sup> To achieve a greater reduction in the burden of CHD, a population approach to increasing the intake of folate is probably required. However it is essential that

intervention trials are conducted to inform policy making.

Finally, if homocysteine represents an aetiological link between NTDs and CHD, other disorders may be similarly related. Other vascular diseases have been alluded to<sup>57</sup> and homocysteine analogues have also been shown to have a role in cancer induction through accumulation of reactive oxygen radicals, changed immunological recognition and increased growth potential of oncogenes.<sup>74</sup> The public health significance of disturbed homocysteine metabolism, and the ways in which it is subject to modification by dietary or genetic means, will undoubtedly be the subject of intensive scientific scrutiny in the early years of the next millennium.

Conflicts of interest: none.

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