RESEARCH

The effect of folic acid based homocysteine lowering on cardiovascular events in people with kidney disease: systematic review and meta-analysis

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Abstract

Objective To systematically review the effect of folic acid based homocysteine lowering on cardiovascular outcomes in people with kidney disease.

Design Systematic review and meta-analysis.

Data sources Medline, Embase, the Cochrane Library, and ClinicalTrials.gov to June 2011.

Study selection Randomised trials in people with non-dialysis dependent chronic kidney disease or end stage kidney disease or with a functioning kidney transplant reporting at least 100 patient years of follow-up and assessing the effect of folic acid based homocysteine lowering therapy. No language restrictions were applied.

Data extraction Two reviewers independently extracted data on study setting, design, and outcomes using a standardised form. The primary endpoint was cardiovascular events (myocardial infarction, stroke, and cardiovascular mortality, or as defined by study author). Secondary endpoints included the individual composite components, all cause mortality, access thrombosis, requirement for renal replacement therapy, and reported adverse events, including haematological and neurological events. The effect of folic acid based homocysteine lowering on outcomes was assessed with meta-analysis using random effects models.

Results 11 trials were identified that reported on 4389 people with chronic kidney disease, 2452 with end stage kidney disease, and 4110 with functioning kidney transplants (10 951 participants in total). Folic acid based homocysteine therapy did not prevent cardiovascular events (relative risk 0.97, 95% confidence interval 0.92 to 1.03, $P=0.326$) or any of the secondary outcomes. There was no evidence of heterogeneity in subgroup analyses, including those of kidney disease category, background fortification, rates of pre-existing disease, or baseline homocysteine level. The definitions of chronic kidney disease varied widely between the studies. Non-cardiovascular events could not be analysed as few studies reported these outcomes.

Conclusions Folic acid based homocysteine lowering does not reduce cardiovascular events in people with kidney disease. Folic acid based regimens should not be used for the prevention of cardiovascular events in people with kidney disease.

Introduction

People with kidney disease of any severity experience excess cardiovascular events and mortality compared with the general population. High plasma homocysteine levels increase as estimated glomerular filtration rate levels decline with the prevalence of hyperhomocysteinaemia (defined in relation to the upper limit of the reference range), reported to be 36-89%

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Search strategy

Supplementary table and figures

in patients with chronic kidney disease depending on severity,¹⁻³ 70-75% in those with functioning kidney transplants,⁴⁻⁵ and 85-100% in those with end stage kidney disease.⁶⁻¹⁰ High homocysteine levels have been associated with an increased risk of cardiovascular events¹¹ in the general population, with a 25% lower homocysteine level associated with an 11% lower risk of coronary artery disease and a 19% lower risk of stroke.¹² The direct relation between homocysteine levels and cardiovascular events observed in the general population has led to the hypothesis that reducing homocysteine levels could reduce the burden of cardiovascular disease. However, studies of homocysteine lowering in the general population have failed to show clear cardiovascular benefits.¹³⁻¹⁶ Moreover, one study in people with a history of myocardial infarction suggested harm with use of a combination of folic acid, vitamin B₁₂, and vitamin B₆.¹³

The lack of benefit in the general population contrasts with that seen in people with homocysteinuria, where therapy prevents cardiovascular events.¹⁷ A key distinction between the two populations is the level of homocysteine, which is noticeably higher (100-400 µmol/L) in people with homocysteinuria than in people with cardiovascular disease or diabetes (mean 13 µmol/L¹³⁻¹⁴). Homocysteine levels in people with kidney disease lie between those of the general population and those with classic homocysteinuria.¹⁹ This has led to the hypothesis that homocysteine lowering may be useful in people with kidney disease, despite the lack of benefit in the broader population, and has driven the conduct of randomised trials in this patient group. A meta-analysis of eight large trials using individual patient level data found the lack of effect of homocysteine lowering to be consistent across categories of renal function.²⁰ That study utilised serum creatinine levels rather than an estimate of glomerular filtration rate to assess renal function and compared the impact of relatively mild differences in renal function (serum creatinine concentrations <80, 80-94, and ≥95 µmol/L).

We undertook a systematic review and meta-analysis to examine the effects of folic acid based homocysteine lowering compared with placebo or control treatments on cardiovascular events and other clinical outcomes in people with a range of severity of kidney disease, including kidney transplant recipients and those with non-dialysis dependent chronic kidney disease and end stage kidney disease.

Methods

A systematic review of the literature was carried out according to PRISMA²¹ guidelines for the conduct of meta-analyses of intervention trials. We searched Medline via Ovid (1950 to June 2011), Embase (1966 to June 2011), and the Cochrane Library database (Cochrane central register of controlled trials), using relevant text words and medical subject headings that included all spellings of homocysteine, folic acid, vitamin B, cardiovascular disease, kidney disease, renal dialysis, and kidney transplantation (see supplementary file for search strategy). The search was limited to randomised clinical trials in any language. To identify any other relevant studies we manually scanned the reference lists of identified trials and review articles and searched the clinicaltrials.gov website for additional studies. When necessary we contacted authors or principal investigators for original data.

Study selection

Two reviewers (MJJ, AK) independently searched the literature, extracted data, and assessed the quality of trials using a

standardised approach and a prespecified protocol (available from the corresponding author). We considered for inclusion all completed randomised controlled trials assessing the effects of folic acid based homocysteine lowering therapy on cardiovascular outcomes in people with kidney disease (including those receiving maintenance dialysis or with a functioning kidney transplant) and with a minimum of 100 patient years of follow-up. Studies with a sequential or crossover design were excluded. We considered studies to be eligible if they compared folic acid based homocysteine lowering therapy with placebo or usual care or if they compared a higher dose of folic acid based homocysteine lowering therapy with a lower dose. Chronic kidney disease was defined as the National Kidney Foundation kidney disease outcomes quality initiative chronic kidney disease stage 3-4 (that is, an estimated glomerular filtration rate of 15-59 mL/min/1.73 m²), or as defined by study authors. End stage kidney disease was defined as an estimated glomerular filtration rate of less than 15 mL/min/1.73 m², the requirement for dialysis, or as defined by study authors. A functioning kidney transplant was defined as a kidney transplant in situ with no requirement for maintenance dialysis. The outcomes assessed were prespecified, and included cardiovascular events (defined as myocardial infarction, stroke, and cardiovascular death), all cause mortality, cardiovascular mortality, myocardial infarction, stroke, leg amputation, dialysis access thrombosis, and the start of renal replacement therapy among participants not requiring dialysis. Data on adverse events were collected, including gastrointestinal, dermatological, neurological, and malignant events.

Data extraction and quality assessment

Using a standardised form two reviewers (MJJ, AK) extracted data on participant characteristics (age, sex, study population, severity of kidney disease, presence of diabetes, or history of cardiac disease, defined as previous myocardial infarction or as defined by study authors), intervention characteristics, baseline and achieved mean homocysteine levels, mean duration of follow-up, and numbers of outcome events. Data were extracted according to intention to treat principles. One study in people with functioning renal transplants reported both intention to treat analyses and analyses censored for loss of transplant function,²² therefore we used the intention to treat data in these analyses. The quality of the study report was determined by assessing concealment of treatment allocation; blinding of outcome assessors, care providers, and participants; completeness of study and follow-up; and intention to treat analysis.²³ Potential small study bias was assessed with the Harbord test²⁴ and represented graphically with Begg funnel plots of the natural log of the relative risk versus its standard error.²⁵ Disagreements on abstracted data were resolved by consensus and involvement of a third reviewer (VP) when necessary.

Data synthesis and analysis

We obtained summary estimates of overall and subgroup relative risk ratios using a random effects model. Analyses were done with the metan command using reported raw event counts where possible, or otherwise using reported relative risk estimates. The I² statistic was used to estimate the percentage of variability across studies attributable to heterogeneity beyond chance.²⁶ Subgroup heterogeneity was estimated by the Cochran C test, with studies weighted using the inverse variance method. Prespecified subgroup analyses included classification of kidney disease, study intervention (folic acid alone versus folic acid plus B group vitamins), baseline homocysteine level (more or

less than 20 $\mu\text{mol/L}$, the approximate 95th centile for homocysteine in men and women in the United States²⁷), background fortification, proportion of study participants with diabetes at baseline (more or less than the approximate median), proportion of study participants with cardiac disease at baseline (more or less than the approximate median), whether the overall study population was recruited on the basis of kidney disease, average follow-up time (more or less than the approximate median, 30 months), study event number (more or less than the approximate median, 150 events), and composite definition (the prespecified definition of myocardial infarction, stroke, or cardiovascular death, or other definition according to the study authors).

We considered a P value of less than 0.05 as significant for all analyses. Statistical analyses were carried out with Stata 11.0 (Stata; TX, USA).

Results

The search yielded 359 articles, of which 36 were reviewed in full text (fig 1). Eleven randomised trials provided information on 10 951 participants with kidney disease, totalling 4389 with stage 3-4 chronic kidney disease, 2452 with end stage kidney disease, and 4110 with functioning kidney transplants (table 1). Trials were reported between 2004 and 2011, with additional data provided by the authors for one study.⁸ Trial participants consisted entirely of people with end stage kidney disease for four trials,^{6 9 28 29} both end stage kidney disease and chronic kidney disease in two trials,^{7 8} and people with a functioning kidney transplant in one trial.²² Three papers reported on subgroups of chronic kidney disease from larger trials of vascular disease or diabetes,³⁰ survivors of myocardial infarction,³¹ and survivors of stroke or transient ischaemic attack,³² where chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 $\text{ml/min}^{30 31}$ or a serum creatinine concentration greater than 120 $\mu\text{mol/L}$.³² One trial was carried out in people with diabetic nephropathy, defined as the coexistence of diabetes and albuminuria (minimum 300 mg/day) or proteinuria (minimum 500 mg/day).³³ One trial was excluded as it compared two different methods of homocysteine lowering therapy (50 mg intravenous 5-methyltetrahydrofolate three times a week compared with 5 mg oral folic acid daily) rather than comparing with placebo or comparing different dose intensities.³⁴

The mean age of trial participants was between 48.5 and 72.2 years (table). The proportion of trial participants who were male ranged from 50% to 98% (median 64%), the proportion with a diagnosis of diabetes ranged from 11% to 100% (median 40%), and the proportion with a history of cardiac disease ranged from 11% to 100% (median 34%). Follow-up ranged from 24 to 60 months (median 38 months, table).

Baseline homocysteine levels were increased at baseline and were reduced by folic acid based therapy (table). The mean difference in homocysteine levels between treated and control participants was $-4.97 \mu\text{mol/L}$ (95% confidence interval -9.44 to -0.49) in the five studies reporting the requisite data for the calculation.^{8 9 22 30 33} Homocysteine levels were reduced into the normal range ($\leq 12 \mu\text{mol/L}$) in only two studies, both of which were carried out in populations with milder degrees of renal dysfunction.^{22 30}

The interventions were predominantly based on daily oral folic acid supplementation in doses of between 2.5 mg and 40 mg (table). Cointerventions included supplementation with B group vitamins (seven trials, 9852 participants). Seven trials compared an intervention with placebo, one compared an intervention with usual care (no placebo), and three compared an intervention

with low dose vitamins (table). One trial consisted of a three way comparison of high (15 mg), medium (5 mg), and low (1 mg) dose daily oral folic acid supplementation.⁶ For the purposes of the current analysis the high and medium dose arms were combined and compared with the low dose arm. One trial that recruited people with a functioning kidney transplant reported both analyses on outcomes censored three months after the start of dialysis and outcomes of intention to treat analyses,²² of which the intention to treat analyses were selected for our review. Baseline mean homocysteine levels ranged from 15.6 to 47 $\mu\text{mol/L}$. Five trials reported achieved mean homocysteine levels, which ranged from 11.9 to 22.6 $\mu\text{mol/L}$ in the intervention group. Four trials were done on a background of fortification of grain with folic acid, whereas one was done with partial fortification of grain.

Effect of homocysteine lowering therapy on outcomes

Cardiovascular events

Ten studies reported 3045 cardiovascular events among 10 863 participants (fig 2). Homocysteine lowering therapy had no overall effect on cardiovascular events (relative risk 0.97, 95% confidence interval 0.92 to 1.03, $P=0.326$). There was no evidence of heterogeneity across the included studies ($I^2=0.0\%$, $P=0.467$ for heterogeneity).

Supplementary figure 2 shows the effects on secondary outcomes. Homocysteine lowering did not affect cardiovascular mortality (six trials, 5968 participants, relative risk 0.97, 95% confidence interval 0.82 to 1.16, supplementary figure 3), all cause mortality (nine trials, 8772 participants, 1.02 0.95 to 1.10, supplementary figure 4), myocardial infarction (eight trials, 8586 participants, 0.96, 0.84 to 1.11, supplementary figure 5), or stroke (eight trials, 8586 participants, 0.95, 0.75 to 1.21, supplementary figure 6), with no heterogeneity overall or between different categories of kidney disease.

Homocysteine lowering did not affect rates of access thrombosis (three trials, relative risk 0.96, 95% confidence interval 0.83 to 1.11, supplementary figure 7). In addition, homocysteine lowering therapy did not reduce rates for start of renal replacement therapy in people with non-dialysis dependent chronic kidney disease (two studies, 1543 participants, relative risk 1.05, 95% confidence interval 0.95 to 1.16) or a functioning kidney transplant (one study, 4110 participants, 1.12, 0.91 to 1.37, supplementary figure 8).

Tolerability of homocysteine lowering agents

Adverse event rates were reported by seven trials (supplementary figure 9). Homocysteine lowering had no effect on adverse event rates (relative risk 1.00, 95% confidence interval 0.92 to 1.08, $P=0.93$). The rates of reported adverse events varied noticeably between studies, ranging from 1.8% (adverse events leading to withdrawal from study treatment)⁶ to 89.1% (adverse events including "many transient minor complaints, such as dizziness, nausea or headache").³³ Some trials reported only malignancies.^{9 30} We were unable to complete planned separate analyses of gastrointestinal, dermatological, neurological, and malignant events owing to the small number of trials reporting these outcomes.

Subgroup analyses

The impact of folic acid based homocysteine lowering on cardiovascular events did not differ significantly in any of the subgroups studied (fig 3). Patient characteristics examined

included kidney disease classification ($P=0.785$ for heterogeneity), baseline homocysteine levels ($P=0.368$ for heterogeneity), the proportion with diabetes ($P=0.346$ for heterogeneity), and the proportion with cardiac disease ($P=0.741$ for heterogeneity). Trial characteristics studied included the intervention (use of folic acid compared with folic acid plus B group vitamins: $P=0.568$ for heterogeneity), the type of study (primary chronic kidney disease versus subgroup of larger study: $P=0.877$ for heterogeneity), the average follow-up time ($P=0.342$ for heterogeneity), the number of events in the study ($P=0.637$ heterogeneity), and the use of a predefined cardiovascular composite endpoint ($P=0.815$ for heterogeneity). The effect of any exposure to folic acid in the controls was assessed through background folic acid fortification in the studied population ($P=0.121$ for heterogeneity) and through any exposure either by background fortification or by trial administered low dose folic acid ($P=0.204$ for heterogeneity). Continuous variables (baseline homocysteine levels, trial proportion with diabetes, trial proportion with cardiac disease, average follow-up time, and number of events in the study) were also explored using metaregression in sensitivity analyses, with results confirming that none of these factors had a significant impact on the overall meta-analysis (results not shown).

Quality

Trials were overall of high quality (supplementary table 1) with the method of sequence generation clear in eight of the 11 studies and explicit details of allocation concealment in 10 studies. Participants, study staff, and outcome assessors were blinded in 10 studies. There was low risk of bias as a result of outcome reporting and selective outcome reporting in all 11 trials. Evidence of small study publication bias was lacking (Harbord test $P=0.850$).

Discussion

In this large systematic review including over 10 000 participants with kidney disease, randomisation to folic acid based homocysteine lowering therapy did not affect the incidence of cardiovascular events, all cause mortality, cardiovascular mortality, myocardial infarction, stroke, requirement for dialysis treatment, or access thrombosis. There was no evidence of harm, defined by rates of adverse events in people with kidney disease, although this conclusion should perhaps be interpreted with caution given the noticeable variation in definitions and rates of adverse events reported in the trials. These outcomes were consistent across categories of kidney disease (end stage kidney disease, chronic kidney disease, and functioning kidney transplant), with no evidence of heterogeneity. Many people with kidney disease seem to be receiving folic acid supplementation³⁵ and some guidelines recommend supplementation of folic acid and B group vitamins or of water soluble vitamins in people with kidney disease on prudential grounds.^{36 37} Our findings suggest that folic acid based homocysteine lowering therapy should not be used for the prevention of cardiovascular events in people with kidney disease, a population in whom drug burden is often high.

Comparison with systematic reviews of homocysteine lowering in all populations

These data are consistent with studies in the general population, where folic acid based homocysteine lowering has also not been found to prevent cardiovascular events in large randomised trials. Previous systematic reviews have analysed the effect of folic acid based homocysteine lowering in the general population

as successive trials have been reported. In 2006, a meta-analysis of 12 randomised trials reported no effect on the risk of cardiovascular disease, coronary heart disease, stroke, or all cause mortality.¹⁵ The possibility of benefit for stroke outcomes was raised in 2007 in a meta-analysis of eight trials (relative risk 0.82, 95% confidence interval 0.68 to 1.00, $P=0.045$).³⁸ More recently, the VITATOPS trial carried out in people with recent stroke or transient ischaemic attack found no significant effect on cardiovascular events (relative risk 0.91, 95% confidence interval 0.82 to 1.00, $P=0.05$) or stroke (0.92, 0.81 to 1.06).³² The addition of the VITATOPS results to those of previous studies again found no reduction in cardiovascular events, stroke (0.94, 0.86 to 1.01), or myocardial infarction.³²

An individual patient meta-analysis was published by the B-Vitamin Treatment Trialists' Collaboration in 2010 of 37 485 participants in eight trials randomised to folate containing B vitamins or to control for the prevention of vascular disease.²⁰ The meta-analysis showed that folic acid supplementation had no impact on major vascular events, mortality, or cancer incidence despite an average 25% reduction in homocysteine levels. There was no evidence of heterogeneity in subgroup analyses comparing the impact of the intervention according to serum creatinine concentrations (<80 , 80-94, and ≥ 95 $\mu\text{mol/l}$). The trialists' analysis included 4361 participants contained in the current analysis, representing 12% of the individual patient data meta-analysis and 40% of the current report. The additional 6590 participants included in the current report are from studies published after the previous report (4603 participants) or from studies that did not meet the 1000 participant criteria of the former report (1987 participants). These studies have effectively excluded any beneficial cardiovascular effect of homocysteine lowering therapy in the general population, and the current review adds to this evidence by similarly excluding meaningful benefit in kidney disease.

Comparison with previous systematic reviews of homocysteine-lowering in people with kidney disease

A previous systematic review of folic acid based homocysteine lowering in people with advanced or end stage kidney disease reported a reduction in all fatal and non-fatal cardiovascular events (seven trials, 3886 participants, relative risk 0.85; 95% confidence interval 0.76 to 0.96; $P=0.009$) and no significant reduction in a composite of myocardial infarctions, stroke, and cardiovascular death (five trials, 3619 participants, 0.87, 0.75 to 1.00, $P=0.06$), with the point estimate favouring the intervention but with some imprecision.³⁹ Differences between the analyses include the near threefold higher number of participants in the current review (10 951 in 11 trials compared with 3886 in seven trials in the previous analysis) through the inclusion of all kidney disease categories, permitting a broader study population. Our study included all reports of outcomes for patients with kidney disease randomised to homocysteine lowering to comprehensively summate the available evidence, permitting the inclusion of the post hoc analysis of HOPE-2.³⁰ Additionally the two studies had methodological differences. The previous meta-analysis summated the separate reports for various cardiovascular outcomes (for example, myocardial infarction, stroke, sudden cardiac death) to derive a figure for a composite of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular cause resulting in the potential for some participants to contribute to the outcome more than once. In our analysis we elected to use the trial definition where this study's composite was not reported. The different approach to the treatment of the composite accounts for most of the

difference between ours and the previous report, with the risk ratio falling from 0.972 (95% confidence interval 0.902 to 1.047) to 0.880 (0.762 to 1.015) in the four studies where both methods can be tested. We believe the findings of the current review are likely to be a better estimate of the true effect of folic acid based homocysteine lowering on cardiovascular outcomes. Further information and precision could be gained from analysis of all completed trials through the conduct of further analyses using data at individual patient level.

Impact of folic acid on homocysteine lowering in people with and without kidney disease

Doses of 0.8 mg of folic acid or more are required to achieve maximal homocysteine lowering of a standardised 23% reduction in trials of participants where folic acid dose was compared with homocysteine reduction.⁴⁰ The addition of vitamin B₁₂ increased the degree of homocysteine lowering to 30%. In 25 trials of homocysteine lowering utilising 0.8 mg folic acid or higher, homocysteine was lowered to 12 µmol/L or less in treated participants in all but two studies, and one of these was carried out in participants with kidney disease.⁴¹ Conversely among the trials of the current analysis, homocysteine levels were largely not normalised despite doses of folic acid substantially greater than 0.8 mg being administered, a finding that has been shown previously.^{41 42} It has been postulated that the relative resistance of patients with end stage kidney disease to folic acid based therapy may be due to impaired folic acid metabolism and impaired folate absorption as well as impaired renal clearance.⁴³

Observed relation of homocysteine levels with cardiovascular events in people with kidney disease

Adding further strength to these conclusions, earlier reports of clear relations between homocysteine levels and cardiovascular events in people with kidney disease⁴³ have been challenged by more recent studies observing no association^{44 45} or even an inverse association.¹⁰ A meta-analysis of observational studies in end stage kidney disease found no association between homocysteine levels and clinical events in retrospective studies, whereas prospective studies showed no association with all cause mortality but a positive association with cardiovascular events, which increased by 9% with every 5 µmol/L increase in homocysteine levels. These observations of the risks associated with various homocysteine levels led in part to the generation of the “reverse epidemiology hypothesis,” which asserts altered risk factor patterns may be confounded by the poor nutrition and inflammatory state common in patients requiring dialysis such that the association of homocysteine and outcomes is driven by nutritional state.^{46 47} Another explanation supported by some^{45 48 49} but not all^{5 50 51} analyses, is that homocysteine is simply a marker of kidney function. Regardless of the nature of the association reported by observational studies, it is now clear that interventions to lower homocysteine levels in people with kidney disease do not lead to a reduction in cardiovascular events.

Impact of background fortification on homocysteine lowering

The relative risk of cardiovascular events was 0.91 (95% confidence interval 0.81 to 1.02) in trials where controls had no exposure to folic acid based regimens, compared with 0.99 (0.93 to 1.06) in trials where controls did have some level of exposure, either through fortification or through comparator treatment.

The difference was not significant ($P=0.24$ for heterogeneity). The individual patient data meta-analysis of eight large trials found that folic acid based therapy had no impact on major vascular events, whether administered against a background of fortification (relative risk 0.99 99% confidence interval 0.90 to 1.09) or not (1.02, 0.96 to 1.09).²⁰ Short of further randomised trials, individual patient level data analysis of participants in all homocysteine lowering trials according to kidney disease status may increase analysis power providing greater clarity.

Strengths and limitations of the review

The strengths of this systematic review are its rigorous methodology, the importance of the clinical question, and the clear result. The findings have direct implications for the management of hundreds of millions of people with kidney disease around the world, including millions receiving dialysis for end stage kidney disease, many of whom are currently taking folic acid supplements. Limitations include the reliance on tabular data rather than individual patient level data. Some studies used different definitions for the primary outcome of cardiovascular events, although this did not seem to meaningfully impact the findings. We could only include results for people with kidney disease included in larger trials where these are reported, raising the possibility of reporting bias. However this would be expected to exaggerate any benefit and none was found. Furthermore, the definition of chronic kidney disease varied among the studies (see table).

Conclusion

In summary, folic acid based homocysteine lowering does not prevent cardiovascular events in people with kidney disease and consideration should be given to discontinuing its use for cardiovascular prevention in this population.

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Contributors: MJJ contributed to the study design, screened articles, extracted data, performed statistical analyses and drafted and revised the paper. AK contributed to the study design, sourced articles, screened articles, extracted data and revised the paper. SZ contributed to the study design, obtained data from one of the trials, and revised the paper. SDN contributed to the study design and revised the paper, TN contributed to the study design, performed statistical analyses and revised the paper, SUN contributed to the study design, extracted data and revised the paper, MPG contributed to the study design and revised the paper, AC contributed to the study design and revised the paper, GS contributed to the study design and revised the paper, VP initiated the study, contributed to the study design and revised the paper. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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What is already known on this topic

Elevated homocysteine levels are associated with an increased risk of cardiovascular events

Homocysteine lowering in the general population has failed to show clear cardiovascular benefits unlike the situation with people with homocysteinuria who have noticeably increased homocysteine levels

Homocysteine levels increase as estimated glomerular filtration rate levels decline

What this study adds

In over 10 000 people with a range of severity of kidney disease no benefit was seen from folic acid based homocysteine lowering therapy for cardiovascular events, all cause mortality, cardiovascular mortality, myocardial infarction, stroke, requirement for dialysis treatment, or access thrombosis

The results were consistent across categories of kidney disease (end stage kidney disease, chronic kidney disease, and functioning kidney transplant), with no evidence of heterogeneity

Our findings suggest that folic acid based homocysteine lowering should not be used for cardiovascular prevention in people with kidney disease

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that : no support from any organisation for the submitted work; SZ is a member of the advisory boards for MSD, Novo Nordisk, and Boehringer Ingelheim, and has received consultancies from Novo Nordisk and Johnson and Johnson, speakers fees from MSD, Novo Nordisk, Astra Zeneca/BMS, Novartis, Sanofi Aventis, and Servier International, and payment for the development of educational presentations from Medi Mark; MG has received payment for lectures from Roche Pharmaceuticals; SDN has received a KL2 grant from the National Institutes of Health; AC has received payment for lectures from Roche, Servier, AMGEN, and MSD; MJ has received an unrestricted grant from CSL; Concord Hospital has received an educational grant from Shire; VP is a member of the Abbot advisory board, has grants or grants pending from Roche, Johnson and Johnson, Baxter, and Servier and has received payment for lectures from Roche, Servier, and Astra Zeneca; MJ, AK, SZ, TN, MG, AC, and VP are affiliated with the George Institute, which receives funding from various pharmaceutical companies to support parts of its research activities, which companies might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: No additional data available.

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Table

Table 1 | Characteristics of studies reporting effect of folic acid based homocysteine lowering therapy in people with kidney disease

Study	Study population	Category of kidney disease No (%)	Mean age (years)	% male	No (%) with diabetes	No (%) with cardiac disease	Components of cardiovascular composite	Mean homocysteine* (μmol)		Study intervention‡	Comparison	Grain fortification	Mortality (n)
								Baseline	Achieved†				
Wrone 2004 ⁶	ESKD	ESKD 510 (100)	60.2	50	232 (45)	174 (34)§	Myocardial infarction, stroke, death, coronary revascularisation, transient ischaemic attack, carotid endarterectomy, amputation	32.9	24.9	15 mg or 5 mg folic acid daily¶	1 mg folic acid	Yes	80
Zoungas 2006 ⁹ (ASFAST)	ESKD and CKD	ESKD 267 (85); CKD 48 (15)**	56.2	68	73 (23)	35 (11)††	Myocardial infarction, stroke, cardiovascular death	27	21.5‡‡	15 mg folic acid	Placebo	No	80
Righetti 2006 ⁹	ESKD (HD)	ESKD 88 (100)	64.6	56	17 (19)	51 (58)§	Myocardial infarction, stroke, sudden cardiac death, angina, carotid endarterectomy in patients with symptoms§§	34.6	22.6	Folic acid 5 mg daily or 2nd daily according to folic acid levels+vitamin B complex 2nd daily (B ₁ 250 mg, B ₂ 250 mg, B ₁₂ 500 mg) if plasma B ₁₂ depleted	Usual care	No	80
Jamison 2007 ⁷ (HOST)	ESKD and CKD	ESKD 751 (37); CKD 1305 (63)¶¶	65.8	98	1129 (55)	511 (25)††	Myocardial infarction, stroke, all cause mortality, amputation	24.1	17.8	40 mg folic acid, 100 mg vitamin B ₆ , 2mg vitamin B ₁₂ daily	Placebo	Yes	80
Vianna 2007 ²⁹	ESKD	ESKD 186 (100)	48.5	59	42 (23)	44 (24)§	Myocardial infarction, stroke, cardiovascular death, arrhythmias, angina, heart failure	25.0‡‡	NR	10 mg folic acid 3 times per week after haemodialysis	Placebo	No	80
Mann 2008 ³⁰ (HOPE 2)***	Vascular disease or DM (CKD 11%)	CKD 619 (100)†††	72.2	67	269 (43)	537 (87)§	Myocardial infarction, stroke, cardiovascular death	15.8	11.9	2.5 mg folic acid, 50 mg vitamin B ₆ , 1 mg vitamin B ₁₂	Placebo	Partial†††	80
House 2010 ³³ (DIVINE)	Diabetic nephropathy§§§	CKD 238 (100)	60.4	75	238 (100)	74 (31.1)§	Myocardial infarction, stroke, all cause mortality, revascularisation	15.5	13.3	2.5 mg folic acid, 25 mg vitamin B ₆ , 1 mg vitamin B ₁₂	Placebo	Yes	80
Armitage 2010 ³¹ (SEARCH)***	History of myocardial infarction	CKD 1686 (100)†††	64.2¶¶¶¶	83¶¶¶¶	1267 (11)¶¶¶¶	1686 (100)†††¶¶¶¶	Myocardial infarction, stroke, coronary heart disease death, revascularisation	NR	NR	2 mg folic acid, 1 mg vitamin B ₁₂	Placebo	No	80
Heinz 2010 ²⁸	ESKD	ESKD 650 (100)	61.0	58	262 (40)	312 (48)	Myocardial infarction, stroke, sudden cardiac death, unstable angina, revascularisation, peripheral arterial disease, pulmonary embolism,	29	18.8	5 mg folic acid, 50 μg B ₁₂ , 20 mg B ₆ after haemodialysis	0.2 mg folic acid, 4 μg B ₁₂ , 1 mg B ₆ after haemodialysis	No	80

(continued)

Study	Study population	Category of kidney disease No (%)	Mean age (years)	% male	No (%) with diabetes	No (%) with cardiac disease	Components of cardiovascular composite	Mean homocysteine* (µmol)		Study intervention‡	Comparison	Grain fortification	BMJ first published as 10.1136/bmj.e3533 on 13 June 2012. Downloaded from http://www.bmj.com/ on 26 April 2023 by guest. Protected by copyright.	M for (n)
								Baseline	Achieved†					
Hankey 2010 ³² (VITATOPS)***	Stroke or TIA in preceding 7 months	CKD 493 (100)††††	62.6¶¶¶¶	64¶¶¶¶	1899 (24)¶¶¶¶	598 (7)‡‡‡¶¶¶	thromboses excluding shunt thromboses Myocardial infarction, stroke, cardiovascular death	NR	NR	2 mg folic acid, 25 mg vitamin B ₆ , 0.5 mg vitamin B ₁₂	Placebo	Partial‡‡‡		4
Bostom 2011 ²² (FAVORIT)	Kidney transplant recipients	KTR 4110 (100)	52	63	1663 (40.5)	820 (20.0)§	Myocardial infarction, stroke, cardiovascular disease death, resuscitated sudden death, revascularisation, above ankle amputation, repair of abdominal aortic aneurysm	16.4	11.8‡‡‡‡	5 mg folic acid, 50 mg B ₆ , 1 mg B ₁₂	1.4 mg B ₆ , 2.0 µg B ₁₂	Yes		4

CKD=predialysis chronic kidney disease; ESKD=dialysis dependent end stage kidney disease; KTR=functioning kidney transplant recipient; NR=not reported.

*Homocysteine levels not included if not available for subgroup with chronic kidney disease.

†In intervention group.

‡Daily unless stated otherwise.

§Cardiac disease as defined by study author.

¶¶Study design had two intervention arms and one "standard care" arm. For the current analysis, two intervention arms are combined.

**Non-dialysis dependent chronic kidney disease, defined as serum creatinine concentration ≥ 0.4 mmol/L.

††Cardiac disease defined as previous myocardial infarction.

§§Cardiovascular composite not reported separately for randomised and observed participants.

¶¶¶Chronic kidney disease defined as Cockcroft-Gault estimated glomerular filtration rate ≤ 30 ml/min.

‡‡Median reported.

***Chronic kidney disease subgroup of larger trial.

†††MDRD estimated glomerular filtration rate < 60 ml/min. Participants with severe renal disease (serum creatinine level $> 2 \times$ upper limit of normal) were excluded by design.

‡‡‡Grain fortification in some but not all trial countries.

§§§Participants with chronic kidney disease stage 4 and 5 were excluded by design.

¶¶¶¶Data for chronic kidney disease subgroup not available, data for total study reported.

****Mean reported.

††††Chronic kidney disease defined as serum creatinine concentration > 120 µmol/L.

‡‡‡‡Based on a sample of 72 participants in the intervention group.

Figures

Fig 1 Identification process for eligible studies

Fig 2 Effect of folic acid based homocysteine lowering therapy on composite cardiovascular events

Fig 3 Subgroup analyses for effect of homocysteine lowering on cardiovascular events. Data reported as "not available" applied to chronic kidney disease subgroups of relevant studies