Preventive health care, 2000 update: screening and management of hyperhomocysteinemia for the prevention of coronary artery disease events

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Abstract

Objective: To establish guidelines for the screening and treatment of hyperhomocysteinemia in the investigation and management of coronary artery disease (CAD).

Options: Measurement of plasma total homocysteine (tHcy) levels in the fasting state or 4–6 hours after oral methionine load; vitamin supplementation with folic acid and vitamins B6 and B12; adherence to the recommended daily allowance of dietary sources of folate and vitamins B6 and B12.

Outcomes: This article reviews the available evidence on the association between plasma tHcy levels and CAD and the effect of lowering tHcy levels through vitamin supplementation or dietary intake.

Evidence: MEDLINE was searched for relevant English-language articles published from January 1966 to June 1999; also reviewed were additional articles identified from the bibliographies.

Benefits, harms and costs: Cardiovascular disease is the leading cause of death in Canada. Homocysteine, generated in the metabolism of methionine, may have a role in the development of cardiovascular disease. The prevalence of hyperhomocysteinemia in the general population is between 5% and 10% and may be as high as 30%–40% in the elderly population. If population-based studies are correct, tHcy may be responsible for up to 10% of CAD events and thus may represent an important and potentially modifiable risk factor for cardiovascular disease. Laboratory testing for tHcy is currently restricted to research centres, and costs range from $30 to $50 per person. Newer, less costly techniques have been developed and should become readily available with time.

Values: The strength of evidence was evaluated using the methods of the Canadian Task Force on Preventive Health Care.

Recommendations: Although there is insufficient evidence to recommend the screening or management of hyperhomocysteinemia at present (grade C recommendation), adherence to recommended daily allowance of dietary sources of folate and vitamins B6 and B12 should be encouraged. If elevated tHcy levels are discovered, vitamin deficiency should be ruled out to allow specific treatment and prevention of complications, such as neurological sequelae due to vitamin B12 deficiency. Experts in the field advocate treatment of elevated tHcy levels in high-risk people, such as those with a personal or family history of premature atherosclerosis or a predisposition to develop hyperhomocysteinemia. Definitive guidelines for the management of hyperhomocysteinemia await the completion of randomized trials to establish the effect of vitamin supplementation on CAD events.

Validation: The findings of this analysis were reviewed through an iterative process by the members of the Canadian Task Force on Preventive Health Care.

Sponsors: The Canadian Task Force on Preventive Health Care is funded through a partnership between the Provincial and Territorial Ministries of Health and Health Canada.
Cardiovascular disease is the leading cause of death in Canada, accounting for almost 40% of all deaths. Although rates of death from ischemic heart disease are declining, the costs to society remain high. Since a number of cardiovascular deaths may be preventable, the search for novel risk factors continues. Homocysteine is an intermediate that is generated in the metabolism of methionine (Fig. 1). Several intriguing observations suggest a role for homocysteine in the development of vascular disease. People who have homocystinuria, an autosomal recessive disorder, have severe hyperhomocysteinemia, premature atherosclerosis and thromboembolic complications. Furthermore, homocysteine may promote the oxidation of low-density lipoprotein cholesterol, vascular smooth muscle cell proliferation, platelet and coagulation factor activation, and endothelial dysfunction. Therefore, altered homocysteine metabolism has become the focus of increasing attention because of its potential role in the pathogenesis of atherosclerosis and other conditions, such as venous thrombosis.

The prevalence of hyperhomocysteinemia in the general population is between 5% and 10%, according to a threshold set at the 90th or 95th percentile (about 15 µmol/L). However, rates may be as high as 30%–40% in the elderly population. If the results from population-based studies are correct, then up to 10% of events due to coronary artery disease (CAD) may be attributable to elevated plasma homocysteine levels. Thus, homocysteine may represent an important and potentially modifiable risk factor for cardiovascular disease.

The purpose of this review was to evaluate the quality of evidence pertaining to homocysteine and CAD events and to make recommendations regarding the screening and management of hyperhomocysteinemia.

Methods

A computerized search of MEDLINE for English-language articles published between January 1966 and June 1999 was conducted using the MeSH (medical subject heading) terms “homocysteine,” “hyperhomocysteinemia,” “methionine,” “coronary disease,” “arteriosclerosis,” “myocardial ischemia,” “folic acid,” “vitamin B₁₂,” “vitamin B₉,” and “pyridoxine” in various combinations. Relevant articles were also identified through a manual review of references. Where possible, the highest level of evidence was sought; hence, abstracts, cross-sectional studies, case reports and case series were not included. Studies concerning other types of vascular disease were also excluded.

The evidence was reviewed systematically using the methodology of the Canadian Task Force on Preventive Health Care. The task force, comprised of expert clinicians and methodologists from a variety of medical specialties, used a standardized evidence-based method (Appendix 1) for evaluating the effectiveness of this intervention. The final recommendations were arrived at unanimously by an expert panel and principal author. Feedback from 2 content experts was incorporated into a final draft of the manuscript before submission for publication. Procedures to achieve adequate documentation, consistency, comprehensiveness, objectivity and adherence to the task force’s methodology were main-

![Fig. 1: Biochemical pathways of homocysteine metabolism. Ser = serine; Gly = glycine; MTHF = methylenetetrahydrofolate; MTHFR = N⁵,N¹⁰-methylenetetrahydrofolate reductase; THF = tetrahydrofolate; SAM = S-adenosylmethionine; SAH = S-adenosylhomocysteine; DMG = dimethylglycine; CβS = cystathionineβ-synthase.](image-url)
Hyperhomocysteinemia and coronary artery disease

...tained at all stages during review development, the consensus process and production of the final manuscript. The full methodology has been described previously.  

Screening tests for hyperhomocysteinemia

Most assays measure levels of total homocysteine (tHcy) (protein-bound and complexed moieties) in the fasting state or 4–6 hours after an oral methionine load (0.1 mg/kg). High-pressure liquid chromatography, the most common method, has a coefficient of variation of 3%–11%. Samples must be placed immediately on ice to avoid spurious elevations in tHcy levels. Furthermore, levels are falsely low in the acute phase of illness such as myocardial infarction (MI). Current screening tests cost between $30 and $50; however, newer, less costly techniques for measuring tHcy levels have been developed and should become readily available with time.

Aside from genetic predisposition, a number of factors raise plasma tHcy levels, including increasing age, male sex and elevated serum creatinine levels. Drugs such as antiepileptic agents, methotrexate and nitrous oxide and certain disease states such as psoriasis, acute lymphoblastic leukemia, breast cancer and hypothyroidism also increase tHcy levels, likely through effects on vitamin status. Homocysteine is inversely correlated with serum vitamin B₆, vitamin B₁₂ and folate levels. Thus, in populations with a higher prevalence of vitamin B₁₂ deficiency, such as elderly people, the specificity of plasma tHcy as a cardiac risk factor may be reduced.

Association between homocysteine and risk of CAD events

Retrospective studies

Over 30 case–control studies have compared tHcy levels between CAD patients and healthy control subjects. Patients with CAD had significantly higher fasting plasma tHcy levels in 22 of 27 studies (odds ratio [OR] 1.2–10.9 after adjustment for other cardiac risk factors). Levels after methionine load were also higher in patients with CAD in 8 of 9 studies (adjusted OR 1.3–6.7). Measurement of serum levels yielded similar results. Moreover, 2 meta-analyses of retrospective data confirmed these findings: the odds ratios of CAD associated with elevated plasma tHcy levels were 1.7 (95% confidence interval [CI] 1.5–1.9) and 6.14 (95% CI 2.74–13.73). The relation between tHcy levels and the number of occluded coronary vessels was not consistent.

It is possible that some other factor predisposes to both CAD and hyperhomocysteinemia. As anticipated, cardiac risk factors were more common among patients with CAD. Volunteer bias may exaggerate this difference because participants of clinical trials tend to be healthier and thus control subjects may have fewer risk factors than do people in the general population. Certain healthy behaviours, such as low caffeine intake and multivitamin use, are inversely associated with plasma tHcy levels. Homocysteine may be related to risk factors such as smoking, hypertension, dyslipidemia and hyperglycemia; however, it appears to have an independent effect and may even interact with other factors to influence CAD risk. In one study adjustment for plasma fibrinogen abolished the association between tHcy and CAD. The relation between tHcy and other unconventional risk factors is unknown. Thus, retrospective studies can show an association but not a causal relation.

Prospective studies

Eight nested case–control studies prospectively evaluated the relation between tHcy and the occurrence of a first major CAD event or new-onset angina necessitating coronary artery bypass surgery. Unfortunately, these studies had conflicting findings. MI and coronary death were associated with higher tHcy levels in only 4 of 7 studies and adjustment for prevalent CAD attenuated this relation in 1 study. In the MRFIT trial, a minority of patients who had early CAD events had sufficient frozen plasma available to measure tHcy levels. Thus, in many cases, plasma tHcy may have been measured too far in advance. In

<table>
<thead>
<tr>
<th>Plasma tHcy level, µmol/L</th>
<th>No. of subjects n = 587</th>
<th>Overall mortality, %</th>
<th>Relative risk (and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 9</td>
<td>130</td>
<td>3.8</td>
<td>1.0 (1.0–1.0)</td>
</tr>
<tr>
<td>9–14.9</td>
<td>372</td>
<td>9.9</td>
<td>1.9 (0.7–5.1) 2.3 (0.7–7.7)</td>
</tr>
<tr>
<td>15–19.9</td>
<td>59</td>
<td>25.4</td>
<td>2.8 (0.9–9.0) 2.5 (0.6–10.5)</td>
</tr>
<tr>
<td>≥ 20</td>
<td>26</td>
<td>26.9</td>
<td>4.5 (1.2–16.6) 7.8 (1.7–35.1)</td>
</tr>
</tbody>
</table>

Source: abridged from Nygård et al.  
Note: CI = confidence interval.  
*Adjusted for age, sex, left ventricular ejection fraction, creatinine level, total cholesterol level, extent of CAD, treatment for hypertension, history of diabetes mellitus, smoking history, platelet count and use of ASA.  
†Adjusted for age, sex, left ventricular ejection fraction, creatinine level, total cholesterol level and extent of CAD; p for trend = 0.01.
contrast to major CAD events, the development of angina was not related to plasma tHcy.66

Prospective cohort studies suggest that tHcy is a greater risk factor for major CAD events in patients with established CAD. In 2 studies57,58 coronary events occurred more frequently in men with hyperhomocysteinemia than in men with normal tHcy levels; however, adjustment for prevalent CAD at baseline attenuated this association. In contrast, nonfasting tHcy levels were independently related to death due to cardiovascular disease (relative risk [RR] 1.52, 95% CI 1.16–1.98) and overall mortality (RR 1.54, 95% CI 1.31–1.82) in elderly men and women from the original Framingham cohort.59 The most compelling evidence comes from Nygård and associates,60 who prospectively followed 587 patients with significant stenosis on coronary angiography. A dose–response relation between baseline homocysteine levels and both death due to CAD and overall mortality was observed (Table 1). Similar findings were noted among patients with other forms of atherosclerosis.61

The evidence from the prospective studies suggests that homocysteine acts by promoting acute thromboembolic events. Few prospective studies have evaluated the role of homocysteine in the chronic progression of atherosclerosis. In the Shunt Occlusion Trial62 graft occlusion rates 1 year after coronary artery bypass surgery were not related to preoperative tHcy levels. However, atherosclerotic changes incurred by tHcy may require longer than 1 year to develop. In summary, the evidence strongly suggests that plasma tHcy is a risk factor for acute cardiac events in patients with underlying vascular disease.

### Association between genetic predisposition to hyperhomocysteinemia and CAD

Homozgyosity for a mutation in the 5,10-methylene-tetrahydrofolate reductase (MTHFR) gene, involved in homocysteine metabolism, is found in 4%–14% of the general population and is associated with elevated plasma tHcy levels under conditions of impaired folate status.63–66 The importance of this mutation in the development of CAD may depend on the population. Studies involving Japanese people have consistently shown a higher prevalence of the mutation among patients with CAD,68–71 whereas only a minority of studies involving whites detected an association.65,66 Moreover, a relation between the MTHFR genotype and the number of occluded vessels on coronary angiography was observed in Japanese patients69 but not in whites.72–74 No association between the mutation and other risk factors, including a family history of premature CAD, has been shown.71–74

In one meta-analysis, involving almost 5000 patients from 8 studies, the homozygous mutation was associated with an increased risk of CAD (OR 1.22, 95% CI 1.01–1.47).67 However, a larger meta-analysis of 23 studies failed to demonstrate an association between the MTHFR genotype and either CAD (OR 1.11, 95% CI 0.91–1.37) or any cardiovascular end point (OR 1.12, 95% CI 0.92–1.37).67 A Japanese study found a declining prevalence of the MTHFR mutation with increasing age; this finding suggests that the mutation may lead to early deaths due to cardiovas-

### Table 2: Summary table of recommendations (screening and treatment of hyperhomocysteinemia)

<table>
<thead>
<tr>
<th>Manoeuvre</th>
<th>Effectiveness</th>
<th>Level of evidence*</th>
<th>Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening for plasma tHcy level†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population</td>
<td>An association between tHcy levels and CAD risk has been shown (the majority of studies measured fasting tHcy levels). However, the effect of screening on patient outcomes is unknown</td>
<td>Cohort§ and case–control∥ studies (II-2)</td>
<td>Insufficient evidence to recommend for or against screening for hyperhomocysteinemia in the general population (grade C)</td>
</tr>
<tr>
<td>People at high risk for CAD events</td>
<td>Prospective studies have shown a more consistent relation between tHcy levels and CAD events in patients with pre-existing CAD. Again, the effect of screening on patient outcomes is unknown</td>
<td>Cohort§ and case–control∥ studies (II-2)</td>
<td>Insufficient evidence to recommend for or against screening for hyperhomocysteinemia in high-risk populations (grade C)†</td>
</tr>
<tr>
<td><strong>Vitamin therapy</strong></td>
<td>Treatment with folic acid (alone or with vitamin B12) is effective in lowering plasma tHcy levels, whereas vitamin B6 lowers post-methionine load levels. There are no completed studies regarding the effectiveness of treatment on clinical outcomes</td>
<td>RCTs§ (I), cohort study∥ (II-2) and uncontrolled studies∥ (II-3)</td>
<td>Insufficient evidence to recommend for or against treatment of hyperhomocysteinemia with vitamin therapy (grade C)§</td>
</tr>
</tbody>
</table>

Note: RCTs = randomized controlled trials.
*See Appendix 1 for definitions of the levels of evidence and grades of recommendations.
†If fasting state or after methionine load.
‡Screening may identify individuals at higher risk of developing coronary artery disease, leading to aggressive risk factor modification. However, there is insufficient evidence to recommend screening for the purpose of treating hyperhomocysteinemia.
§Although folic acid effectively lowers plasma tHcy levels, there is insufficient evidence to support that its use would prevent CAD events.
cular disease. However, the mutation does not appear to be related to longevity in whites (OR 0.87, 95% CI 0.69–1.11). In light of these observations, it has been suggested that other genetic abnormalities or risk factors may interact with the MTHFR mutation to increase cardiovascular risk.

Association between serum folate, vitamin B₆, or vitamin B₁₂ levels and risk of CAD events

Homocysteine may simply be a nonspecific marker of vitamin deficiency. Several studies identified an inverse relation between serum folate levels and CAD events on univariate analysis; however, adjustment for plasma tHcy levels obliterated this effect. Serum vitamin B₆ levels have no relation to CAD; however, vitamin B₁₂ may be an independent risk factor. Robinson and associates observed an increased risk of CAD among patients with low vitamin B₁₂ levels (OR 1.84, 95% CI 1.39–2.42) that remained after adjustment for plasma tHcy levels. Similarly, homocysteine remained a significant predictor of CAD after controlling for serum vitamin levels.

Effect of vitamin therapy

Several randomized controlled trials have evaluated the

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended daily allowance</th>
<th>Average dietary intake by adults</th>
<th>Dietary sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid</td>
<td>Women: 180 µg, Men: 200 µg</td>
<td>200–300 µg</td>
<td>Green leafy vegetables (e.g., spinach, broccoli), legumes (e.g., lentils, chickpeas, lima beans), orange juice, oranges, cereals, breads, wheat germ</td>
</tr>
<tr>
<td>Vitamin B₆</td>
<td>1.6 mg</td>
<td>1.5 mg</td>
<td>Meat, poultry, fish, green leafy vegetables, legumes, seeds, potatoes, cantaloupe, milk, egg yolks, cereals, grains, wheat, wheat germ</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>2.4 µg</td>
<td>4–8 µg</td>
<td>Beef, poultry, fish (particularly crab, oyster, salmon and herring), liver, kidney, soy, fruit juice, dairy products, egg yolks, fortified cereals, breads</td>
</tr>
</tbody>
</table>

Table 4: Randomized trials of homocysteine-lowering interventions currently underway

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Start date</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergen Vitamin Study</td>
<td>Stroke (Norway)</td>
<td>1997</td>
<td>2000</td>
</tr>
<tr>
<td>Cambridge Heart Antioxidant Study (CHAOS-2)</td>
<td>MI, unstable angina (United Kingdom)</td>
<td>1998</td>
<td>4000</td>
</tr>
<tr>
<td>Heart Outcomes Prevention Evaluation (HOPE-2) Study</td>
<td>Arterial vascular disease (Canada)</td>
<td>1999</td>
<td>5000</td>
</tr>
<tr>
<td>Norwegian Study of Homocysteine Lowering with B-Vitamins in Myocardial Infarction (NORVIT)</td>
<td>MI (Norway)</td>
<td>1998</td>
<td>3000</td>
</tr>
<tr>
<td>Prevention with a Combined Inhibitor and Folate in Coronary Heart Disease (PACIFIC) Study</td>
<td>Arterial vascular disease (Australia)</td>
<td>1998</td>
<td>10 000</td>
</tr>
<tr>
<td>Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)</td>
<td>MI (United Kingdom)</td>
<td>1998</td>
<td>12 000</td>
</tr>
<tr>
<td>Vitamins in Stroke Prevention (VISP) Trial</td>
<td>Stroke (United States)</td>
<td>1998</td>
<td>3600</td>
</tr>
<tr>
<td>VITAmins TO Prevent Stroke Study (VITATOPS)</td>
<td>Stroke (Australia)</td>
<td>1999</td>
<td>5000</td>
</tr>
<tr>
<td>Women’s Antioxidant and Cardiovascular Disease Study (WACS)</td>
<td>Vascular disease or high risk for vascular disease (United States)</td>
<td>1998</td>
<td>8000</td>
</tr>
</tbody>
</table>

Note: MI = myocardial infarction. Source: abridged from Eikelboom et al.
vitamin B6 per day had a lower risk of heart disease than
(10%–14% reduction),97–99 regardless of whether vitamin B6
folic acid per day had a modest effect on fasting tHcy levels
men and women, breakfast cereal fortified with 666
Higher plasma tHcy levels and lower serum folate levels
25% on average in people with or without vascular disease.
revealed that folic acid (0.4–5 mg) lowered tHcy levels by
in the majority
folic acid may be effective. In the majority
(50–250 mg).93,94 In patients who respond poorly to vitamin
-doses of vitamin B12 (0.2–1 mg), lowered fasting plasma tHcy levels by
0.5 mg/d; however, 0.2 mg may be sufficient
to normalize fasting tHcy levels in some patients.90,91
Lower doses, such as 0.1 mg, appear to be ineffective.90,92
Although vitamin B12 was found to have little effect on
folic acid intake to 1 mg/d101,104 or adding higher
doses of vitamin B12 (0.2–1 mg/d)105 because of the theoretical
risk of unmasking occult vitamin B12 deficiency.101

**Prevention of CAD**

Whether lowering plasma homocysteine levels will pre-
vent CAD events is unknown because of the absence of
longer randomized controlled trials with appropriate end
points. Some epidemiological data suggest that folate and
vitamin B, intake may influence the occurrence of major
CAD events. The Nurses’ Health Study100 found that wo-
men who consumed more than 400 µg of folate or 3 mg of
vitamin B, per day had a lower risk of heart disease than
those with lower intake levels (adjusted RR 0.69 for folate,
95% CI 0.55–0.87, and 0.67 for vitamin B, 95% CI
0.53–0.85). Furthermore, an uncontrolled study showed that
areas of plaque in carotid arteries regressed in 38 pa-
patients with hyperhomocysteinemia who were given daily
amounts of folic acid (2.5–5 mg), vitamin B, (25 mg) and
vitamin B12 (250 µg) over 4 years.104 Similarly, in another
study patients with homocystinuria who received a mini-
um of folic acid (5 mg) and vitamin B12 (100–200 mg) ex-
experienced fewer vascular events (RR 0.09, 95% CI 0.02–
0.38) than patients who remained untreated.102 Although
striking, findings from the latter study cannot be extrapo-
lated to the general population because of patient differ-
ences and other methodological issues.

**Recommendations**

**By the Canadian Task Force on Preventive Health Care**

The task force’s recommendations are summarized in
Table 2. There is insufficient evidence to include or exclude
screening of tHcy levels in any population (grade C recom-
pendation). Screening may enable identification of patients
at high risk for CAD so that other risk factors can be man-
egaged aggressively. However, laboratory testing for homocys-
teine is currently restricted to research centres. Moreover,
testing is not yet covered by provincial health insurance, and
therefore patients may be required to cover the cost.

Although folic acid effectively lowers plasma tHcy levels,
there is insufficient evidence to suggest that its use would
prevent CAD events (grade C recommendation). Adher-
ence to the recommended daily allowance of dietary
sources of folate and vitamins B, and B12 (Table 3) may pre-
vent hyperhomocysteinemia due to vitamin deficiency.
Once elevated tHcy levels are discovered, vitamin defi-
ciency should be ruled out to allow specific treatment and
prevention of complications, such as neurological sequelae
due to vitamin B12 deficiency. Some authorities recommend
limiting folic acid intake to 1 mg/d101,104 or adding higher
doses of vitamin B12 (0.2–1 mg/d)105 because of the theoretical
risk of unmasking occult vitamin B12 deficiency.101

**By other groups**

Guidelines from the American Heart Association104 state
that it may be reasonable to screen tHcy levels in people
who are at risk for hyperhomocysteinemia (e.g., those with
renal failure) or in those who have a personal or family his-
tory of premature atherosclerosis. Several experts in the
area concur105,106 and suggest lowering fasting tHcy levels
to less than 10 µmol/L.107 If initial treatment with dietary
sources are ineffective, then supplements or fortified foods
containing at least 400 µg of folic acid, 2 mg of vitamin B, and
6 µg of vitamin B12 can be used.

**Research agenda**

Large-scale randomized trials designed to assess the ef-
effect of folic acid therapy on cardiovascular events are un-
derway107 (Table 4). Thus, evidence on which to base re-
commendations for the treatment of hyperhomocysteinemia
is forthcoming. The optimal vitamin dose and regimen,
and the role of methionine-load testing in the diagnosis of
Hyperhomocysteinemia and coronary artery disease

this disorder need to be clarified. Although folic acid attained through food sources alone may be insufficient to normalize elevated tHcy levels, people with low folate intake are more susceptible to hyperhomocysteinemia. Most flour and cereal products consumed by Canadians are produced domestically, where folic acid fortification is optional. Review of fortification policies will be necessary as our knowledge regarding prevention and treatment of hyperhomocysteinemia advances.

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Competing interests: None declared.

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Hyperhomocysteinemia and coronary artery disease

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Appendix 1: Canadian Task Force on Preventive Health Care Levels of evidence and grades of recommendations

Levels of evidence

I Evidence from at least one well-designed randomized controlled trial

II-1 Evidence from well-designed controlled trials without randomization

II-2 Evidence from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group

II-3 Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here

III Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

Grades of recommendations

A Good evidence to support the recommendation that the condition or manoeuvre be specifically considered in a periodic health examination (PHE)

B Fair evidence to support the recommendation that the condition or manoeuvre be specifically considered in a PHE

C Insufficient evidence regarding inclusion or exclusion of the condition or manoeuvre in a PHE, but recommendations may be made on other grounds

D Fair evidence to support the recommendation that the condition or manoeuvre be specifically excluded from a PHE

E Good evidence to support the recommendation that the condition or manoeuvre be specifically excluded from a PHE

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