# Papers

## Randomised controlled trial of effect of fruit and vegetable consumption on plasma concentrations of lipids and antioxidants

Sarah Zino, Murray Skeaff, Sheila Williams, Jim Mann


### Abstract

**Objectives:** To determine the extent to which plasma antioxidant concentrations in people with habitual low intake of fruit and vegetables respond to increased intakes of these foods. To examine whether advice to increase fruit and vegetables will result in reduction of concentrations of total and low density lipoprotein cholesterol.

**Design:** Randomised controlled trial in which intervention and control groups were followed up for eight weeks. The intervention group was asked to consume eight servings of fruit and vegetables a day.

**Setting:** Dunedin, New Zealand.

**Subjects:** Eighty seven subjects with normal lipid concentrations who ate three or fewer servings of fruit and vegetables daily.

**Main outcome measures:** Plasma concentrations of vitamin C, retinol, α and β carotene, α tocopherol, lipids, and lipoproteins. Dietary intake assessed with diet records over four days.

**Results:** The mean plasma vitamin C, α carotene, and β carotene concentrations increased in parallel with increased dietary intake of fruit and vegetables in the intervention group. Concentrations of retinol, α tocopherol, lipids, and lipoproteins remained unchanged despite some increase in dietary vitamin E and a small reduction in saturated fat intake.

**Conclusions:** Following a recommendation to increase fruit and vegetable consumption produces change in plasma concentrations of vitamin C, α carotene, and β carotene likely to reduce incidence of cancer. More specific dietary advice to modify fat intake may be necessary to reduce the risk of cardiovascular disease mediated by lipoprotein and vitamin E.


### Introduction

Prospective studies suggest that people with high intakes of fruit and vegetables or blood antioxidant concentrations[1 2] in the highest quantile of the distribution have low risks of epithelial cancers,[3] coronary heart disease,[4] and stroke.[5] The anticarcinogenic properties of antioxidants in animal and cell culture systems and their ability to reduce oxidation of low density lipoproteins provide plausible biological explanations for the epidemiological associations.[6 7]

These observations have led to the recommendation that populations with high rates of cardiovascular disease and epithelial cancers should substantially increase dietary antioxidants through increased consumption of fruit and vegetables. A common response to these recommendations has been a dramatic increase in the consumption of antioxidant supplements, despite little evidence of benefit in placebo controlled trials of supplemental β carotene, retinol, α tocopherol, and vitamin C.[8-11] Vitamin E supplementation in patients with atherosclerosis may reduce risk of subsequent myocardial infarction but does not prolong life.[12] The results of these intervention trials suggest that any reduction in the risk of disease associated with high antioxidant nutrient intake may result from consuming a mix of foods rich in antioxidants rather than consuming antioxidants as single nutrients.

There are few data concerning the extent to which increased intake of fruit and vegetables influences antioxidant concentration in the blood, information which is essential for rational dietary recommendations. We report the results of what we believe is the first population based study to examine the effects on blood antioxidant concentrations of increased consumption of fruit and vegetables. The dietary approach used has also enabled us to examine whether increased consumption of fruit and vegetables reduces the intake of saturated fatty acids to an extent which will facilitate lowering of concentrations of total and low density lipoprotein cholesterol.

### Methods

*Subjects*—Ninety volunteers (26 men aged 19-69 years, 64 women aged 18-61 years) were recruited from 120 respondents to advertisements. Subjects had to be healthy with no history of chronic disease; have a total cholesterol concentration of $<7.5$ mmol/l and triglyceride concentration $<3$ mmol/l; not be taking dietary supplements or drugs affecting lipid metabolism; and be consuming three or fewer servings of fruit and vegetables daily. A serving equated to 1 cup raw vegetables, ½ cup cooked vegetables, ¾ cup vegetable juice, 1 medium sized whole fruit (for example, an

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**Table 1** Characteristics of participants at baseline. Values are means (SD) unless stated otherwise

| Detail | Control group (n=43) | Intervention group (n=44) |
|---|---|---|
| Age (years) | 31.9 (11.4) | 28.6 (7.9) |
| No of men | 26 | 36 |
| No of women | 17 | 8 |
| Body mass index (kg/m$^2$) | 25.6 (5.4) | 25.3 (4.1) |
| Cholesterol (mmol/l) | 5.13 (0.97) | 4.72 (0.98) |
| Triglyceride (mmol/l) | 1.48 (0.55) | 1.26 (0.81) |
| No of smokers | 17 | 13 |

apple), ½ cup cooked or canned fruit, or ¾ cup fruit juice.[13] Smokers were not excluded.

*Study design*—After a two week run in during which participants consumed their usual diet, they were randomly assigned, by using random numbers, to intervention and control groups and followed up for eight weeks. Four day diet records were completed during the run in and during week 4. Unannounced 24 hour recalls were obtained at week 6 as an additional measure of compliance. Fasting venous blood samples (20 ml) were collected and body weight recorded at baseline and fortnightly intervals. Eighty seven participants completed the trial, one moved (control) and two withdrew (one intervention, one control). Ethical approval was obtained from the Southern Regional Health Authority, and all subjects gave informed consent.

*Diet*—The control group maintained their usual eating habits whereas the intervention group were instructed to increase consumption of fruit and vegetables to eight servings daily and not to alter consumption of nuts, oil, butter, or margarine. They were given detailed dietary instructions, menu suggestions, and recipes, reinforced during fortnightly individual interviews. Targets were achieved by incorporating vegetables into mixed dishes, soups, salads, and casseroles. Juices were substituted for other drinks and fruits for baked products.

*Laboratory methods*—Plasma samples were stored at −80°C. Lipids and lipoproteins were analysed as described previously for our laboratory.[14] The coefficients of variation were 1.3% for cholesterol, 3.2% for triglycerides, and 3.6% for high density lipoprotein cholesterol. Concentrations of retinol, α tocopherol, and α and β carotene were determined simultaneously with high performance liquid chromatography[15]; precision within batches being 2.0%, 3.9%, 7.3%, and 6.6%, and between batches 2.9%, 5.5%, 8.2%, and 7.1%, respectively. Accuracy was verified by analysis of quality control serum samples from the US National Bureau of Standards. Plasma vitamin C concentration was determined by fluorometric assay.[16] The coefficients of variation within and between batches were 0.7% and 1.6%, respectively.

*Statistical analysis*—A previous pilot study (n = 47) showed an SD of 0.27 μmol/l for β carotene. To detect a difference of 0.2 μmol/l at 90% power (α = 0.05) two groups of 39 subjects were required. For blood analysis, multiple regression was used to examine the difference between the two groups adjusted for age, sex, smoking, body mass index, cholesterol concentration, and the baseline value. For dietary analysis age, sex, and the baseline values were used as covariates. Product moment correlations determined associations between intakes and biochemical indices. Changes in plasma concentrations were calculated as week 8 – baseline and changes in dietary intake as week 4 – baseline. The adjusted correlations were obtained by computing two sets of residuals: residuals from regressing plasma β carotene concentration at week 0 on that at week 8 and residuals from regressing serving number at week 0 on that at week 8. The adjusted correlations were then computed as the simple correlations between these two sets of residuals. All values are reported as means (SD) unless otherwise stated.

**Table 2** Reported consumption of fruit and vegetables based on four day diet records. Values are means (SD) unless stated otherwise

| Detail | Baseline | | Week 4 | | Adjusted difference (95% CI)* |
|---|---|---|---|---|---|
| | Control (n=43) | Intervention (n=44) | Control (n=43) | Intervention (n=44) | |
| Fruit (g) | 37 (51) | 93 (118) | 55 (84) | 256 (132) | 177 (125 to 228) |
| Juice (g) | 25 (68) | 56 (96) | 46 (104) | 413 (283) | 341 (243 to 438) |
| Vegetable (g) | 196 (87) | 228 (127) | 218 (104) | 332 (149) | 104 (47 to 162) |
| Total (g) | 258 (131) | 377 (210) | 319 (183) | 1001 (313) | 630 (510 to 751) |
| No of servings per day† | 1.9 (0.7) | 2.4 (0.9) | 2.1 (1.0) | 7.1 (1.4) | 4.7 (4.2 to 5.2) |

*Between intervention and control groups at week 4, adjusted for age, sex, smoking, and baseline value.†See text for definition of serving.

**Table 3** Mean daily energy and nutrient composition of diets calculated from four day diet records

| Detail | Baseline | | Week 4 | | Adjusted difference (95 % CI)* |
|---|---|---|---|---|---|
| | Control (n=43) | Intervention (n=44) | Control (n=43) | Intervention (n=44) | |
| Energy (MJ) | 8.9 | 9.5 | 8.9 | 9.8 | 1.1 (0.3 to 2.0) |
| Total fat (% MJ) | 36 | 35 | 36 | 32 | –3.5 (–6.1 to –1.0) |
| Fatty acids (% MJ): | | | | | |
| Saturated | 17 | 17 | 17 | 15 | –1.7 (–3.0 to –0.4) |
| Polyunsaturated | 4 | 4 | 4 | 4 | –0.1 (–0.7 to 0.5) |
| Monounsaturated | 12 | 11 | 12 | 11 | –1.5 (–2.6 to –0.4) |
| Carbohydrate (% MJ) | 46 | 47 | 45 | 49 | 4.3 (1.8 to 6.8) |
| Protein (% MJ) | 14 | 14 | 14 | 13 | –0.1 (–1.3 to 1.1) |
| Alcohol (% MJ) | 4 | 5 | 6 | 5 | –0.9 (–3.4 to 1.6) |
| Cholesterol (mg) | 255 | 303 | 253 | 254 | –5.8 (–46.1 to 34.5) |
| Fibre (g) | 17 | 19 | 19 | 25 | 6.2 (2.4 to 10.0) |
| β Carotene (μg) | 1793 | 1995 | 1597 | 4683 | 3312 (2380 to 4245) |
| Vitamin C (mg) | 49 | 85 | 63 | 257 | 164 (128 to 201) |
| Vitamin E (mg) | 6 | 6 | 6 | 9 | 3.2 (2.1 to 4.3) |

*Between intervention and control groups at week 4 adjusted for age, sex, and baseline value.

## Results

The mean (range) age of the 87 subjects was 30.2 (18-69) years, mean (range) body mass index was 25.4 (16.5-43.6) kg/m$^2$, and total cholesterol and triglyceride concentrations were 5.03 (2.15-7.84) mmol/l and 1.29 (0.54-2.76) mmol/l. Table 1 shows characteristics of the two groups. Body mass index remained unchanged throughout the study.

Before randomisation participants consumed 2.2 (0.9) servings of fruit and vegetables, weighing 318 (184) g. Differences between control and intervention groups according to unannounced 24 hour recalls (not reported) were similar to those calculated from diet records (table 2). The percentage of energy from total and saturated fat was lower in the intervention group; the percentage of energy from carbohydrate and dietary fibre and concentrations of β carotene and vitamins C and E were higher (table 3). As antioxidant nutrients have a low correlation with total energy

**Table 4** Mean (SD) plasma concentrations of antioxidants (μmol/l) during study period

| Antioxidant | Week 0 | 2 | 4 | 6 | 8 | Adjusted difference (95% CI)* |
|---|---|---|---|---|---|---|
| **Control (n=43)** | | | | | | |
| β Carotene | 0.34 (0.31) | 0.32 (0.22) | 0.36 (0.29) | 0.35 (0.28) | 0.32 (0.23) | |
| α Carotene | 0.08 (0.08) | 0.08 (0.07) | 0.07 (0.07) | 0.07 (0.06) | 0.07 (0.05) | |
| Vitamin C | 25.55 (21.58) | 23.85 (19.87) | 24.98 (22.14) | 24.07 (19.53) | 25.55 (20.44) | |
| α Tocopherol | 21.13 (5.57) | 22.52 (5.81) | 22.06 (6.04) | 22.06 (5.81) | 21.59 (5.81) | |
| Retinol | 2.01 (0.48) | 2.02 (0.55) | 2.02 (0.49) | 1.96 (0.43) | 1.94 (0.47) | |
| **Intervention (n=44)** | | | | | | |
| β Carotene | 0.34 (0.23) | 0.49 (0.29) | 0.48 (0.28) | 0.47 (0.28) | 0.52 (0.30) | 0.17 (0.10 to 0.23) |
| α Carotene | 0.07 (0.05) | 0.11 (0.08) | 0.10 (0.08) | 0.10 (0.09) | 0.10 (0.07) | 0.05 (0.02 to 0.07) |
| Vitamin C | 33.50 (21.00) | 54.51 (22.71) | 51.10 (22.14) | 52.81 (21.01) | 57.92 (22.14) | 26.15 (18.30 to 34.01) |
| α Tocopherol | 20.66 (6.50) | 22.29 (7.20) | 21.83 (5.34) | 21.36 (5.34) | 20.90 (5.11) | 0.42 (–1.56 to 2.41) |
| Retinol | 1.96 (0.49) | 1.99 (0.49) | 1.94 (0.49) | 1.89 (0.45) | 1.94 (0.46) | 0.07 (–0.13 to 0.28) |

*Between intervention and control groups at week 8 adjusted for age, sex, body mass index, smoking, cholesterol concentration, and baseline value.

intake (β carotene $r=0.11$, vitamin C $r=0.12$) no adjustment was made for energy.[17]

At baseline there were no differences between the groups in plasma antioxidant concentrations; striking differences in concentrations of vitamin C and α and β carotene were, however, apparent throughout the trial (table 4). The control group showed no changes. The concentration of α tocopherol expressed in relation to total cholesterol concentration (μmol α tocopherol/mmol total cholesterol) showed no changes in either group (not reported). Concentrations of lipids and lipoproteins remained unchanged throughout the study (table 5).

In the intervention group, correlations between change in number of servings of fruit and vegetables and change in plasma concentrations of micronutrients were; $r=0.09$ for β carotene ($P=0.55$), $r=0.29$ for α carotene ($P=0.06$), and $r=0.25$ for vitamin C ($P=0.11$). Change in plasma concentration of vitamin C was correlated with change in juice intake in grams ($r=0.37$; $P<0.05$). Change in plasma concentration of α carotene was correlated with change in plasma concentration of β carotene ($r=0.38$; $P<0.05$) and with change in dietary β carotene during the intervention ($r=0.58$; $P<0.001$). Change in dietary β carotene and dietary vitamin C correlated poorly with corresponding changes in plasma ($r=0.19$; $P=0.23$) and ($r=0.27$; $P=0.08$), respectively. The correlation between the residuals obtained when the second variable was regressed on the first was $r=0.32$ ($P<0.05$) for serving number and plasma β carotene.

## Discussion

The participants, all of whom ate few fruits and vegetables, seemed to have little difficulty in substantially increasing consumption of these foods by, on average, an extra five servings or 700 g of fruit and vegetables daily. Reported intake of β carotene and vitamin C increased dramatically. Concomitantly, there were modest increases in consumption of total carbohydrate, dietary fibre, and vitamin E. Small decreases in consumption of total and saturated fat occurred despite the absence of specific advice concerning dietary fat.

The relation between change in plasma α carotene concentration and change in dietary β carotene is reasonably strong. Unfortunately, data on α carotene in New Zealand foods are not available, but α and β carotene do coexist in fruit and vegetables.[18] Thus for α carotene dietary intake seems to be a major determinant of blood concentrations, whereas for plasma vitamin C concentration, juice intake is important. Although the intervention diet resulted in marked increases in plasma β carotene and vitamin C concentrations for the intervention group, the correlation between changes in dietary and plasma concentrations of these nutrients is less striking. This finding for vitamin C is similar to that reported in patients with cancer who increased fruit and vegetable consumption.[19] A wide variation in response to ingested β carotene has been reported previously, and the presence of responders and non-responders has been suggested.[20] Many dietary factors influence digestion and absorption of carotenes.[21] Our data contribute to this discussion, providing some confirmation of individual variation in response and suggesting that measurement of plasma β carotene concentration may not be a particularly good marker of an individual's daily fruit and vegetable consumption. Nevertheless, it is important to emphasise that even without specific advice to increase fruit and vegetables rich in β carotene or vitamin C, a general recommendation to increase fruit and vegetable consumption produces marked increases in plasma concentrations of carotenes and vitamin C.

The recommended dietary change resulted in a modest change in dietary vitamin E, but this was insufficient to influence blood concentrations. Similarly, the small reduction in total and saturated fat did not influence plasma concentrations of lipids and lipoproteins.

### Reduction in risk of cancer

Our main aim was to determine whether increased fruit and vegetable consumption could produce alterations in concentrations of plasma antioxidants which

**Table 5** Mean (SD) plasma lipid concentrations (mmol/l) during study period

| Lipid | Baseline: Control (n=43) | Baseline: Intervention (n=44) | Week 8: Control (n=43) | Week 8: Intervention (n=44) | Adjusted differences (95% CI)* |
|---|---|---|---|---|---|
| Total cholesterol | 5.13 (0.97) | 4.72 (0.98) | 4.94 (1.05) | 4.64 (0.94) | –0.02 (–0.29 to 0.25) |
| LDL cholesterol | 3.18 (0.85) | 2.96 (0.92) | 2.98 (0.92) | 2.83 (0.85) | 0.02 (–0.23 to 0.27) |
| HDL cholesterol | 1.28 (0.38) | 1.19 (0.38) | 1.36 (0.41) | 1.24 (0.41) | –0.08 (–0.15 to 0.001) |
| Triglyceride | 1.48 (0.55) | 1.26 (0.81) | 1.34 (0.50) | 1.26 (0.68) | 0.06 (–0.12 to 0.24) |

*Between intervention and control groups at week 8, adjusted for age, sex, body mass index, and baseline value. LDL=low density lipoprotein. HDL=high density lipoprotein.

might be expected to produce clinical benefit. At least 10 prospective studies have shown that high intakes of fruit and vegetables confer protection against cancer, cardiovascular disease, and stroke.[3 5 22 23] Several studies have examined the relation between plasma antioxidant concentrations and subsequent risk of disease, most notably for lung cancer for which six out seven prospective studies have reported reduced risk for those in the highest quantile of the distribution of plasma β carotene concentrations.[3 22] Different approaches have been used, and the results of the various studies are not directly comparable with our results.

Nevertheless, it is of interest to note that in the Basle study, which used a nested case-control approach, plasma β carotene concentrations of patients with lung cancer were comparable with our baseline measurements, whereas those in the Basle control group were remarkably similar to concentrations reached by the participants who increased their consumption of fruit and vegetables.[24] Results from the Japan-Hawaii cancer study suggest that the effect of the intervention achieved in our study might reduce the relative risk of lung cancer from 2.4 to 1.2.[25] Failure to show a beneficial effect of β carotene supplementation in several large randomised controlled trials suggests the possibility that β carotene may not be the key or sole protective factor but rather a marker for one or more closely related factors.[8-10] Should this be the case, the general dietary recommendation made in this study remains likely to produce considerable benefit in terms of reducing risk of cancer, especially epithelial cancers. Furthermore, on the basis of prospective trials, it would move antioxidant intake of people with low fruit and vegetable consumption into the range of intake associated with reduced risk of disease.[1 4] On the basis of recent findings, Levine *et al* advocate an appreciable increase in the recommended daily allowance for vitamin C from 60 mg to 200 mg, an intake readily achieved by participants in the intervention group.[26]

### Other health benefits

Vitamin E has a powerful effect in reducing oxidation of low density lipoprotein,[27] and several cohort studies have shown that high intakes are associated with reduced risk of cardiovascular disease.[28-30] Nested case-control studies in which concentrations of α tocopherol have been measured in plasma samples have not provided confirmation of the dietary associations[23]; the Cambridge heart antioxidant study of α tocopherol supplementation in people with atherosclerosis, however, suggested that substantial amounts used in this trial could reduce the risk of non-fatal myocardial infarction.[12] While the precise role of α tocopherol in the aetiology and the possible protection against the clinical consequences of coronary artery disease remains to be established, it is clear that a general recommendation to increase fruit and vegetable intake will have little effect on plasma concentrations of α tocopherol, even though the bulk of the dietary intake in the United States is derived from this food group.[31] To increase plasma concentrations of α tocopherol through modification of food intake rather than supplements it seems to be necessary to increase substantially consumption of foods rich in vitamin E such as nuts, margarine, and oils. Similarly, a simple recommendation to increase fruit and vegetable intake is unlikely to cause a large enough reduction in saturated fat intake to reduce concentrations of total and low density lipoprotein cholesterol; more specific dietary advice to modify fat intake is required.

**Key messages**

- Increasing intake of fruit and vegetables raises plasma concentrations of vitamin C and α and β carotene
- These changes in plasma concentrations of antioxidants are probably associated with reduced risk of cancer
- A simple recommendation to increase fruit and vegetable intake has little effect on plasma concentrations of α tocopherol, lipids, and lipoproteins
- More specific dietary advice to modify fat intake may be necessary to reduce risk of cardiovascular disease associated with lipoproteins and vitamin E

It is of interest to note that changes in concentrations of vitamin C and α and β carotene occurred within the first two weeks of the intervention and remained virtually unchanged for the duration of the trial. This suggests that future studies exploring the relations between dietary intake and plasma concentrations of these antioxidants can be of relatively short duration.

### Conclusions

In conclusion, we have shown that people with low consumption of fruit and vegetables can appreciably increase plasma concentrations of α carotene, β carotene, and vitamin C when they follow recommendations to increase their consumption of fruit and vegetables substantially. On the basis of comparison with epidemiological data, the concentrations of plasma antioxidants achieved might be expected to reduce the risk of cancer. On the other hand, plasma α tocopherol concentration is not increased, and plasma concentrations of lipids and lipoproteins are not altered by this recommendation. More specific dietary advice to modify intake of fat sources is probably necessary to reduce the risk of cardiovascular disease associated with lipoproteins and vitamin E.

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# Cohort study of effect of being overweight and change in weight on risk of coronary heart disease in old age

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## Abstract

**Objective:** To evaluate risk of late life coronary heart disease associated with being overweight in late middle or old age and to assess whether weight change modifies this risk.
**Design:** Longitudinal study of subjects in the epidemiological follow up study of the national health and nutrition examination survey I.
**Setting:** United States.
**Subjects:** 621 men and 960 women free of coronary heart disease in 1982-84 (mean age 77 years).
**Main outcome measure:** Incidence of coronary heart disease.
**Results:** Body mass index of 27 or more in late middle age was associated with increased risk of coronary heart disease in late life (relative risk = 1.7 (95% confidence interval 1.3 to 2.1)) while body mass index of 27 or more in old age was not (1.1 (0.8 to 1.5)). This difference in risk was due largely to weight loss between middle and old age. Exclusion of those with weight loss of 10% or more increased risk associated with heavier weight in old age (1.4 (1.0 to 1.9)). Thinner older people who lost weight and heavier people who had gained weight showed increased risk of coronary heart disease compared with thinner people with stable weight.
**Conclusions:** Heavier weight in late middle age was a risk factor for coronary heart disease in late life. Heavier weight in old age was associated with an increased risk once those with substantial weight loss were excluded. The contribution of weight to risk of coronary heart disease in older people may be underestimated if weight history is neglected.


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## Introduction

Being overweight is an important contributor to risk of morbidity in younger people, particularly coronary heart disease.[1 2] In people around age 65 heavier weight is associated with a modest increase in the risk of coronary heart disease,[3 4] but it is unclear whether it is a health hazard for even older people.[5] Clarification of risk associated with being overweight in late life is important as incidence of coronary artery disease increases with age, although it has been proposed that being overweight and weight gain with age carries little risk.[5] In studies of weight change in old age, weight loss rather than weight gain was associated with coronary heart disease[4 6-8] and weight change seemed to obscure the risk associated with being overweight.[4 9]

We examined the effects of being overweight and weight change on coronary heart disease in older men and women. Weights obtained roughly 10 years apart

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were used to estimate the risk of coronary heart disease associated with past and current weight, to determine the prevalence of weight change, to estimate the risk of coronary heart disease associated with weight change, and to evaluate whether weight change modified the estimation of risk associated with weight.

## Subjects and methods

The epidemiological follow up study of the national health and nutrition examination survey I (NHANES I) is a longitudinal study of 14 407 people aged 25-74 in 1971-75.[10 11] Follow up to 1987 included an in person interview in 1982-84 with measurement of weight, pulse, and blood pressure; a telephone interview in 1986 of people aged 55 or older at the time of participation in the original survey; and a telephone interview of all cohort members in 1987. Loss to follow up was less than 1% for those eligible.

For this paper we identified a cohort within the longitudinal study and followed them from 1982 to 1984. This design allowed us to use mainly measured weights to estimate change and more stringent criteria for excluding people with existing coronary heart disease. Mean length of follow up for outcome events was 3.9 (SD 0.8) years.

Our study population was aged 70 to 86 in 1982-84. We studied only white people since there were too few black participants to evaluate an interaction between race and weight. All subjects who had died before 1982-84 (n = 940) or could not be located (n = 3) were excluded. We also excluded 1166 people with coronary heart disease in 1982-84. This was defined as a report of heart failure, heart attack, or treatment for heart disease on interview in 1971-75; reporting at 1982-84 interview that a doctor had diagnosed a heart attack or angina; or discharge from hospital with a diagnosis of ICD-9 codes 410-414.

We excluded people with no data on weight or height in the original study and those with no weight recorded during 1982-84 (n = 18). We did include reported weight for the 7% (110) who did not have weight measured in 1982-84. Mean body mass index was similar for those with estimated weight or with measured weight; reported weight has been shown to be highly correlated with measured weight.[12 13] The final study population consisted of 1581 people: 621 men and 960 women.

New coronary heart disease (ICD-9 codes 410-414) in the cohort up to 1987 was determined from documentation of events in hospital discharge records (218, 83%) or from underlying cause of death on death certificates (45, 17%). There were 263 incident cases of coronary heart disease: 141 in women and 122 in men.

Procedures for measuring height and weight have been described.[14 15] The 1982-84 measurements were considered as current and the 1971-75 measurements as past. We used the height measured in 1971-75 to calculate body mass index ($kg/m^2$) for each point in time. These measures were pooled and sex specific cut off points based on thirds were calculated to be applied to both current and past body mass index, with those in the lowest third used as the reference group.[16] An assessment of the effect of survival on these analyses showed that people excluded because of death were heavier in 1971-75 than those included in the cohort. Thus, our analysis is conservative since high risk heavier people have been excluded.

Weight change was calculated as percentage change from 1971-75 to 1982-84. This allows comparison of equivalent change among people of varying initial weight. We created three categories of weight change: gain of 10% or more, gain of less than 10% to loss of less than 10%, and loss of 10% or more. Those whose weight was relatively stable (gain or loss of less than 10%) were used as the reference group.

We tested the interaction between current body mass index and weight change and past body mass index and weight change. To examine how weight change affected risk of coronary disease associated with current weight, categories of weight change were crossed with categories of current body mass index to create nine analytical strata. We estimated risk of coronary heart disease in these nine strata using the thinnest weight stable group as the reference.

The risk factors for coronary heart disease included as covariates were systolic blood pressure, total cholesterol concentration (measured in 1971-75), and report of diabetes in 1982-84. Correlates of weight change included self rated health (excellent, very good, or good versus fair or poor health); alcohol intake (no intake versus any current alcohol intake); educational attainment ($<9$ years of education versus $\geq 9$ years); three variables estimating level of physical capacity (any difficulty versus no difficulty walking 400 m, level of usual or recreational physical activity (high, moderate, or low), or report of tiredness on usual activities); and report of serious illnesses including history of diabetes, stroke, or cancer.

### Statistical methods

The incidence of and mortality from coronary heart disease were calculated per 1000 person years of follow up. Results were similar for men and women so these groups were combined to increase the statistical power

**Table 1** Relative risk (95% confidence interval) of coronary heart disease in late life according to past and current body mass index and weight change

| | | Past body mass index | | | Current body mass index | | | Weight change | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No of events | Lowest third | Middle third | Highest third | Lowest third | Middle third | Highest third | Loss of ≥10% | −10% to 10% | Gain of ≥10% |
| Women* (n=960) | 141 | 1.0 | 1.1 (0.7 to 1.8) | 1.7 (1.1 to 2.6) | 1.0 | 1.0 (0.7 to 1.5) | 1.2 (0.8 to 1.9) | 1.7 (1.2 to 2.4) | 1.0 | 1.3 (0.7 to 2.4) |
| Men* (n=621) | 122 | 1.0 | 1.4 (0.7 to 2.2) | 1.7 (1.1 to 2.7) | 1.0 | 1.0 (0.7 to 1.6) | 1.0 (0.6 to 1.5) | 1.9 (1.2 to 3.1) | 1.0 | 1.1 (0.5 to 2.1) |
| Combined† (n=15821) | 263 | 1.0 | 1.2 (0.9 to 1.7) | 1.7 (1.3 to 2.1) | 1.0 | 1.0 (0.8 to 1.4) | 1.1 (0.8 to 1.5) | 1.7 (1.3 to 2.3) | 1.0 | 1.2 (0.7 to 1.0) |
| Combined‡ (n =1428) | 233 | 1.0 | 1.2 (0.9 to 1.7) | 1.5 (1.1 to 2.2) | 1.0 | 1.0 (0.7 to 1.4) | 1.1 (0.8 to 1.5) | 1.6 (1.2 to 2.2) | 1.0 | 1.1 (0.6 to 1.8) |

*Adjusted for age, cigarette smoking (current, former, never).
†Adjusted for age, cigarette smoking (current, former, never), and sex.
‡Adjusted for age, cigarette smoking (current, former, never), sex, ever having had diabetes, current systolic blood pressure, past total serum cholesterol concentration (smaller number of subjects reflects missing values on covariates).

for subsequent analyses. Statistical modelling was performed with Cox's proportional hazards models to account for variable follow up time.[17] All models were adjusted for sex, age, and cigarette smoking,[16] although risks based on unadjusted crude rates were quite similar. Models of risk for weight change were adjusted for past body mass index.[18] Final models were adjusted for available risk factors for coronary heart disease. The strength of associations was shown by transformation of β coefficients to estimates of relative risk and calculation of 95% confidence intervals. Relation of variables with weight change were tested by $\chi^2$ association.

Since the study was restricted to a subgroup of the original cohort selected on characteristics which were included in sampling—that is, age and race[19 20]—we have presented unweighted results. Previous analyses of a group of similar age and race showed that weighting had little effect.

## Results

The 621 men and 960 women included had a mean age of 77 (SD 4) years in 1982-84. Cut off points for body mass index were 23.47 and 27.28 for women and 23.97 and 26.96 for men. More women (217, 23%) than men (76, 12%) lost 10% or more of body weight between the first and second measures while about equal proportions gained 10% or more (69 women (7%), 48 men (8%)).

Heavier body mass index in 1971-75 was associated with a 70% increase in the risk of coronary heart disease for both men and women (table 1). Heavier current body mass index was not associated with an increased risk of coronary heart disease in either men or women. Weight loss was associated with an increased risk of coronary heart disease for women (1.7 (95% confidence interval 1.2 to 2.4)) and for men (1.9 (1.2 to 3.1)). Weight gain was not associated with increased risk. Elimination of those who lost 10% or more of body weight increased the relative risk estimate among the heaviest third of current weight from 1.1 to 1.4 (1.0 to 1.9).

For men and women combined the risk associated with current weight was modified by history of weight change (multiplicative interaction term P = 0.03). Risk of coronary heart disease was increased among heavier people who had gained weight and among thinner people who had lost weight (table 2).

We examined level of weight change by selected health characteristics in 1982-84 (table 3). Compared with weight stability, weight loss ⩾10% was related to history of diabetes and stroke, fair or poor health, and more complaints of tiredness. Those losing weight were also less physically active and reported more difficulty walking 400 metres. Those gaining weight had less education, were more likely to be former smokers, and reported more tiredness and difficulty walking distances. Controlling for these factors did not change the relation of weight and weight change with coronary risk.

**Table 2** Joint effects of current body mass index and weight change on relative risk* (95% confidence interval) of coronary heart disease in late life

| | Current body mass index | | |
|---|---|---|---|
| **Weight change** | **Lowest third** | **Middle third** | **Highest third** |
| Gain of ⩾10% | 0.3 (0.04 to 0.8) n=12 | 0.7 (0.3 to 2.0) n=16 | 2.2 (1.3 to 4.0) n=20 |
| –10% to 10% | 1.0 n=162 | 1.1 (0.8 to 1.6) n=177 | 1.2 (0.8 to 1.7) n=158 |
| Loss of ⩾10% | 1.8 (1.2 to 2.8) n=48 | 2.5 (1.5 to 4.1) n=20 | 1.2 (0.5 to 0.8) n=8 |

*Adjusted for age, cigarette smoking (current, former, never), and sex.

**Table 3** Number (percentage) of subjects with selected health characteristics reported in 1982-84 and association of characteristics with weight change between 1971-75 and 1982-84

| | | Weight change | | | |
|---|---|---|---|---|---|
| | **Total sample** | **Loss of ⩾10% (n=293)** | **–10% to 10% (n=1171)** | **Gain of ⩾10% (n=117)** | **P value** |
| History of diabetes (n=1578) | 158 (10) | 52 (18) | 92 (8) | 7 (6) | <0.0001 |
| History of stroke (n=1581) | 49 (3) | 16 (5) | 29 (2) | 4 (3) | 0.03 |
| History of cancer (n=1581) | 167 (11) | 39 (13) | 117 (10) | 11 (9) | 0.23 |
| Systolic blood pressure <140 mmHg (n=1471) | 727 (50) | 136 (54) | 539 (49) | 52 (48) | 0.40 |
| Cigarette smoking status (n=1581): | | | | | |
| Never smoker | 950 (60) | 187 (64) | 703 (60) | 60 (51) | 0.04 |
| Former smoker | 486 (28) | 66 (22) | 337 (29) | 43 (37) | |
| Current smoker | 185 (12) | 40 (14) | 131 (11) | 14 (12) | |
| Currently drinking any alcohol (n=1581) | 862 (55) | 139 (47) | 653 (56) | 70 (60) | 0.02 |
| Less than 9 years' education (n=1581) | 669 (42) | 114 (39) | 495 (42) | 60 (51) | 0.14 |
| Any difficulty walking 400 m (n=1571) | 459 (29) | 125 (43) | 296 (25) | 38 (33) | <0.0001 |
| Less physically active (n=1473) | 343 (77) | 213 (85) | 832 (75) | 85 (79) | 0.001 |
| Report of fair or poor health (n=1483) | 414 (28) | 97 (38) | 288 (26) | 29 (27) | 0.001 |
| Tired (n=1466) | 185 (13) | 51 (20) | 116 (10) | 18 (17) | <0.0001 |

## Discussion

Is heavier weight a risk factor for coronary heart disease in older people? We found a risk associated with being overweight, which suggests that coronary heart disease should be added to the several health risks already associated with heavier weight in very old age.[21 22] We also found that knowledge of current weight may not be sufficient to identify those at risk in old age. Weight change from middle age to old age is also an indicator of risk, particularly for thinner people who had lost weight or heavier people who had gained weight. For survivors to old age, the relative importance of weight in middle age or weight in old age is unclear. However, several studies have shown weight in middle age (which may reflect maximum weight for most people) to be most important in determining risk of coronary heart disease. Without a long term weight history clinical assessment may underestimate the risk of disease in old age.[4 9]

We found that weight gain, while not associated with risk overall, was associated with increased risk of coronary heart disease in heavier people. An association of weight gain with increased risk of coronary heart disease is consistent with theoretical models of the effects of weight on risk factors for coronary heart disease risk[23] and recent findings in younger women.[24] Why weight loss is associated with an increased risk of coronary heart disease is unclear, since weight loss should decrease the level of cardiovascular risk factors.[25 26] Although direct information on reasons for weight loss were not included in our data, sustained weight loss in old age is unlikely to be voluntary[27] and may reflect other diseases, some of which might increase the risk of thromboembolic events. For instance, people with diabetes and stroke

**Key messages**

- Little is known about the effects of being overweight (defined as a body mass index of ⩾27) in old age on risk of heart disease
- In this study older people who were overweight had an increased risk of coronary heart disease once weight history was accounted for
- Weight history, particularly in late middle age, is important in assessing risk of coronary disease in older people
- Older heavier people who gained more than 10% of midlife body weight or thinner older people who had lost 10% or more of body weight show high risk compared with thinner people with stable weight

were disproportionately represented in the group that lost weight. Those with weight loss were also less likely to be physically active. Although controlling for these measures did not change the results, further investigation with more frequent weight measurements, reasons for weight loss, and physiological indicators of health would be useful.

**Methodological issues**

Our case ascertainment was based primarily on diagnoses at hospital discharge.[4] Reliance on the death certificate alone might be more likely to falsely attribute cases to coronary heart disease. However, exclusion of cases ascertained by death certificate only did not change our results. Silent myocardial infarction is common among older people and could result in missed cases. However, the prognosis for myocardial infarction is similar regardless of presentation.[28] These cases of coronary heart disease should have been identified when patients were admitted to hospital for later cardiac complications or at the time of death.

There was also a potential for misclassification of current body mass index since current height is likely to be shorter than past height. Since height loss depends on unknown risk factors adjustment for mean height loss might introduce bias. We therefore elected to use the earlier measured value.

**Conclusions**

Heavier weight was a risk factor for coronary heart disease in this group of old men and women, although the association of current weight with risk was modified by weight history. Weight change was common, particularly weight loss. Weight history from middle age added to understanding health risk in late life. Neglect of weight history may lead to underestimation of the importance of being overweight as a risk factor in old age.

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*Endpiece*

## Dr Johnson on overinterpretation of the mini mental state examination

There is a wicked inclination in most people to suppose an old man decayed in his intellects. If a young or middle-aged man, when leaving company, does not recollect where he laid his hat, it is nothing; but if the same inattention is discovered in an old man, people will shrug up their shoulders, and say, "His memory is going."

James Boswell, *The Life of Samuel Johnson*

# Secular trend in the occurrence of asthma among children and young adults: critical appraisal of repeated cross sectional surveys

Per Magnus, Jouni J K Jaakkola


## Abstract

**Objectives:** To review repeated surveys of the rising prevalence of obstructive lung disease among children and young adults and determine whether systematic biases may explain the observed trends.
**Design:** Review of published reports of repeated cross sectional surveys of asthma and wheezing among children and young adults. The repeated surveys used the same sampling frame, the same definition of outcome variables, and equivalent data collection methods.
**Setting:** Repeated surveys conducted anywhere in the world.
**Subjects:** All repeated surveys whose last set of results were published in 1983 or later.
**Main outcome measures:** Lifetime and current prevalences of asthma and current prevalence of wheezing. The absolute increase (yearly percentage) in the prevalences of asthma and wheezing was calculated and compared between studies.
**Results:** 16 repeated surveys fulfilled the inclusion criteria. 12 reported increases in the current prevalence of asthma (from 0.09% to 0.97% a year) and eight reported increases in the current prevalence of wheezing (from 0.14% to 1.24% a year). Changes in labelling are likely to have occurred for the reporting of asthma, and information biases may have occurred for the reporting of wheezing. Only one study reported an increase in an objective measurement.
**Conclusions:** The evidence for increased prevalences of asthma and wheezing is weak because the measures used are susceptible to systematic errors. Until repeated surveys incorporating more objective data are available no firm conclusions about increases in obstructive lung disease among children and young adults can be drawn.


## Introduction

There is widespread belief that the prevalence of asthma is increasing in industrialised societies, particularly in children. This belief stems from results of epidemiological studies. Changes in diagnostic labelling and the presence of selection or information bias can lead to false interpretation of changes in repeated prevalence studies. We reviewed published studies on recent secular trends in asthma in the light of these potential sources of error. We limited the review to repeated cross sectional studies of asthma in children and young adults in which the last set of results was published in 1983 or later.

## Materials and methods

### Inclusion of studies

We included only repeated cross sectional studies that used the same methodology (definition of variables, wording of questions, and methods of data collection) on samples of children or young adults in the same geographic area. Furthermore, both the sampling frame and the sampling method had to be identical within studies. Surveys based on attendance at health care centres (for example, hospital admissions or consultations in general practice) were excluded because time trends for these data depend on the selection of subjects as well as on organisational efficiency, diagnostic methods, and data registration practices over time. Because the mortality from asthma is low and mortality depends on both the incidence of asthma and the case fatality rate we did not include mortality studies.

We excluded some reports because of non-equivalent methods of data collection or content of information, non-equivalent sampling, or lack of specification of sample sizes. For instance, the NHANES studies changed the wording of the question on asthma from "Did a doctor ever tell you that you had asthma" to "Has [name of child] ever been treated for the following? Asthma (Yes, No)."[1] Peat *et al* changed questionnaires between surveys.[2] A study from Aberdeen reported changes between 1964 and 1989 but was excluded because the first data collection was by interview and the second by questionnaire, and the wording of questions was changed.[3] In addition, studies of Israeli[4] and Finnish conscripts[5] were excluded because sample sizes were not given. We also excluded studies in which the sampling frame was not equivalent on the two occasions.[6-8]

To identify studies for inclusion, abstracts of all studies referenced in Medline from January 1983 to April 1996 were extracted if they included "asthma" or "wheezing" combined with words such as "prevalence," "occurrence," "incidence," "increase," or "trend." Sixteen repeated cross sectional studies fulfilled the criteria for inclusion.[9-24] Six studies were from the United Kingdom, four from New Zealand or Australia, two from Israel, two from Scandinavia, one from Taiwan, and one from the United States (table 1). Twelve studies concerned children and four were based on young adults.

### Variables

We extracted three measures of disease prevalence from the studies: lifetime occurrence (cumulative incidence) of asthma, current asthma, and current wheezing. For current wheezing, studies asked either for symptoms during a defined retrospective period (12 months or three years) or for the presence of symptoms recently or occasionally. Data collection methods for children were primarily based on

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**Table 1** Country, time period, population, data collection methods, outcome measures, and operational definitions used in repeated cross sectional studies of asthma and wheezing

| Reference | Country and time period | Population | Data collection method | Outcome measure | Operational definition |
|---|---|---|---|---|---|
| **Children** | | | | | |
| Mitchell (1983)[9] | New Zealand 1968-82 | 11-13 Year old schoolboys and schoolgirls | Questionnaires filled in by parents | Lifetime asthma | "Has this child suffered from asthma?" |
| Shaw *et al* (1990)[10] | New Zealand 1975-89 | 12-18 Year old schoolboys and schoolgirls | Questionnaires filled in by pupils, and interviews | Lifetime asthma, current asthma, current wheeze | One or more episodes labelled by student as asthma. Wheeze without label of asthma and not just associated with colds |
| Mitchell and Asher (1994)[11] | New Zealand 1985-91 | 7-10 Year old schoolboys and schoolgirls | Questionnaires filled in by parents | Lifetime asthma, current wheeze | "Has your child ever had wheeze?" "How long is it since your child had wheeze?" Asthma question not specified |
| Peat *et al* (1994)[12] | Australia 1982-92 | 8-10 Year old schoolboys and schoolgirls | Questionnaires filled in by parents, and clinical examination | Lifetime asthma, current asthma, current wheeze | Parents asked whether child ever had asthma diagnosed by doctor and whether child had wheezing recently. Current asthma means both recent wheeze and bronchial hyperresponsiveness |
| Hsieh and Shen (1988)[13] | Taiwan 1974-85 | 7-15 Year old schoolboys and schoolgirls | Questionnaires filled in by parents, and screening by paediatricians | Current asthma | At least three attacks of wheezing and dyspnoea in past 12 months |
| Taylor and Newacheck (1992)[14]† | United States 1981-8 | 0-17 Year old boys and girls in population based sample | Interviews of parents or other adult family member | Current asthma | "Did the child have asthma in the last 12 months?" |
| Burr *et al* (1989)[15] | Wales 1973-88 | 12 Year old schoolboys and schoolgirls | Questionnaires filled in by parents | Lifetime asthma, current asthma, current wheeze | Current asthma for children with asthma who also reported wheezing during past 12 months |
| Hill *et al* (1989)[16] | England 1985-8 | 4-11 Year old schoolboys and schoolgirls | Questionnaires filled in by parents | Current asthma, current wheeze | "What have you been told is wrong with your child?" was basis for current asthma |
| Anderson *et al* (1994)[17] | England 1978-91 | 7-8 Year old schoolboys and schoolgirls | Questionnaires filled in by parents | Current wheeze | "Has your child ever had asthma?" If no, "Has he or she ever had attacks of wheezing in the chest?" Recorded number of attacks of asthma or wheezing illness over past 12 months |
| Rona *et al* (1995)[18] | Scotland and England 1982-92 | 5-11 Year old schoolboys and schoolgirls | Questionnaires filled in by parents | Current asthma, current wheeze | "Has he or she suffered from either asthma or bronchitis in the last 12 months" "Does his or her chest ever sound wheezy or whistling?" |
| Omran and Russell (1996)[19] | Scotland 1989-94 | 8-13 Year old schoolboys and schoolgirls | Questionnaires filled in by parents | Lifetime asthma, current wheeze | Reported diagnosis of asthma. "Has your child had a wheezy chest in the last three years?" |
| Rimpela *et al* (1995)[20] | Finland 1977-91 | 12-18 Year old adolescent boys and girls in population based surveys | Questionnaires filled in by adolescents | Current asthma | "Have you had any of the following physician-diagnosed chronic diseases?" (asthma one alternative) |
| **Young adults** | | | | | |
| Laor *et al* (1993)[21] | Israel 1980-9 | 17-18 Year old male and female conscripts | Physical examination | Current asthma | Medical history and examination, results of spirometry and exercise testing |
| Auerbach *et al* (1993)[22] | Israel 1986-90 | 17 Year old male conscripts | Physical examination | Lifetime asthma, current asthma | Medical history and examination, results of spirometry and exercise testing |
| Bruce *et al* (1993)[23] | Northern Ireland 1972-89 | 18-21 Year old male and female university students | Questionnaire and examination by physician | Current asthma | Recording of asthma in records or history of wheeze or dyspnoea triggered by specific allergen or exertion or treatment with antiasthmatic agents. Symptoms during past 12 months |
| Åberg (1989)[24] | Sweden 1971-81 | 18 Year old male conscripts | Questionnaire and examination by physician | Current asthma | Not given |

†These data were also reported by Weitzman *et al* 1992.[25]

questionnaires completed by parents whereas studies of young adults also relied on physical examination. Operational definitions of asthma and wheezing were usually not specified, and the implicit definitions (wording of questions) differed between studies. Table 1 briefly describes the data collection methods, outcome measures, and definitions of asthma and wheezing.

### Statistical methods

For each study the absolute changes in prevalence (percentage change yearly) were estimated from the published figures. The 95% confidence intervals for these estimates were based on weighted linear regression (if more than two years were studied) or on the Poisson distribution for calculating the standard error of the difference between two prevalences. The relative increase over time was studied by the ratio of the prevalence rates at the first and last surveys (with 95% confidence intervals calculated by Taylor series) for both asthma and wheezing.

## Results

### Asthma

Table 2 shows the absolute prevalences for each survey as well as the yearly increase in prevalence. The prevalence of lifetime occurrence of asthma ranged from 5.5% to 31.8% whereas the prevalence of current asthma showed less variability. For lifetime asthma the absolute increase in prevalence ranged from 0.35% to 2.08% yearly. For current asthma the increase ranged from 0.09% to 0.97%. All studies showed increasing prevalences. The increases were in general lower for young adults. Figure 1 shows the absolute yearly increases in the prevalence of current asthma by country and time period. The studies from the United Kingdom found very different degrees of increase. The two studies with the most recent start found the largest yearly increases.

### Wheezing

Only studies in the United Kingdom, Australia, and New Zealand reported current wheeze. The prevalence

**Table 2** Percentage prevalences of lifetime occurrence of asthma, current asthma, and current wheezing, with yearly absolute change in prevalence for 16 repeated cross sectional studies using same methodology

| Reference | Sample size (year; No of respondents) | Lifetime asthma (%) | Yearly change (95% CI) | Current asthma (%) | Yearly change (95% CI) | Current wheezing (%) | Yearly change (95% CI) |
|---|---|---|---|---|---|---|---|
| **Children** | | | | | | | |
| Mitchell (1983)[9] | 1968; 952 | 7.1 | | | | | |
| | 1982; 858 | 13.5 | 0.46 (0.24 to 0.67) | | | | |
| Shaw *et al* (1990)[10] | 1975; 715 | 8.0 | | 5.0 | | 4.6 | |
| | 1989; 435 | 13.3 | 0.38 (0.09 to 0.66) | 8.0 | 0.21 (–0.01 to 0.44) | 6.9 | 0.16 (–0.05 to 0.37) |
| Mitchell and Asher (1994)[11] | 1985; 1 084 | 14.2 | | | | 14.8 | |
| | 1991; 1 901 | 16.3 | 0.35 (–0.13 to 0.83) | | | 18.7 | 0.65 (0.15 to 1.15) |
| Peat *et al* (1994)[12] | 1982; 1 487 | 11.0 | | 5.6 | | 13.0 | |
| | 1992; 1 668 | 31.8 | 2.08 (1.76 to 2.40) | 10.5 | 0.49 (0.29 to 0.69) | 25.4 | 1.24 (0.94 to 1.54) |
| Hsieh and Shen (1988)[13] | 1974; 23 678 | | | 1.3 | | | |
| | 1985; 147 373 | | | 5.1 | 0.34 (0.33 to 0.36) | | |
| Taylor and Newacheck (1992)[14] | 1981; 15 416 | | | 3.2 | | | |
| | 1988; 17 110 | | | 4.3 | 0.16 (0.10 to 0.22) | | |
| Burr *et al* (1989)[15] | 1973; 818 | 5.5 | | 4.2 | | 9.8 | |
| | 1988; 965 | 12.0 | 0.43 (0.25 to 0.61) | 9.1 | 0.33 (0.17 to 0.48) | 15.2 | 0.36 (0.14 to 0.58) |
| Hill *et al* (1989)[16] | 1985; 3 675 | | | 6.0 | | 11.5 | |
| | 1988; 13 544 | | | 8.9 | 0.97 (0.65 to 1.28) | 12.8 | 0.43 (0.02 to 0.85) |
| Anderson *et al* (1994)[17] | 1978; 4 147 | | | | | 11.1 | |
| | 1991; 3 070 | | | | | 12.9 | 0.14 (0.01 to 0.26) |
| Rona *et al* (1995)[18] | 1982; 9 304 | | | 3.3 | | 11.3 | |
| | 1992; 9 539 | | | 8.9 | 0.56 (0.49 to 0.63) | 15.8 | 0.45 (0.35 to 0.56) |
| Omran and Russell (1996)[19] | 1989; 3 403 | 10.2 | | | | 19.8 | |
| | 1994; 4 034 | 19.6 | 1.88 (1.53 to 2.23) | | | 25.4 | 1.12 (0.69 to 1.55) |
| Rimpela *et al* (1995)[20] | 1977-9; 4 335 | | | 1.0 | | | |
| | 1991; 3 059 | | | 2.8 | 0.14 (0.09 to 0.19) | | |
| **Young adults** | | | | | | | |
| Laor *et al* (1993)[21] | 1981-3; 134 863 | | | 1.7 | | | |
| | 1984-6; 144 491 | | | 2.2 | | | |
| | 1987-9; 163 832 | | | 3.3 | 0.28 (0.28 to 0.28) | | |
| Auerbach *et al* (1993)[22] | 1986; 13 363 | 7.9 | | 5.0 | | | |
| | 1990; 21 807 | 9.6 | 0.43 (0.27 to 0.58) | 5.9 | 0.23 (0.10 to 0.35) | | |
| Bruce *et al* (1993)[23] | 1972; 1 384 | | | 1.3 | | | |
| | 1978; 1 469 | | | 1.4 | | | |
| | 1983; 1 683 | | | 2.2 | | | |
| | 1986; 1 768 | | | 2.2 | | | |
| | 1989; 2 046 | | | 2.8 | 0.09 (0.03 to 0.15) | | |
| Åberg (1989)[24] | 1971; 55 393 | | | 1.9 | | | |
| | 1981; 57 150 | | | 2.8 | 0.09 (0.07 to 0.11) | | |

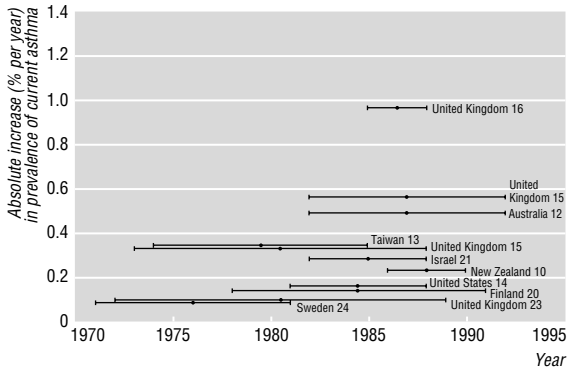


**Fig 1** Absolute yearly increases in prevalence of current asthma in 12 repeated cross sectional studies by country and time period. Bars indicate first and last survey years of each study. Points are midyears

of current wheezing varied from 4.6% to 25.4%. The absolute yearly increase in the prevalence of current wheezing ranged from 0.14% to 1.24%. Studies started after 1980 showed the largest absolute yearly increases in prevalence of wheezing (fig 2).

The five studies that included both current asthma and current wheezing are listed in table 3, which shows the relative increase in both measures. In the New Zealand study current asthma increased by 60% and current wheezing by 50%. In that study and the study from Australia asthma and wheezing increased proportionally. In contrast, all three studies from the United Kingdom showed a larger increase in the prevalence of current asthma than in the prevalence of current wheezing.

## Discussion

Apparent increases in the prevalence of asthma and wheezing over time was found in all the reviewed studies. The degree of increase differed substantially between the studies, even those within the same country. In Australia and New Zealand the increases in asthma and wheezing were proportional whereas in the United Kingdom asthma increased comparatively more than wheezing. Before concluding that real increases in obstructive lung disease among children and young adults have been taking place in these

**Table 3** Relative secular increase (prevalence at last survey over prevalence at first survey) for asthma and wheezing, and ratio between increase for asthma and wheezing

| Reference | Country | Prevalence ratio for current asthma (95% CI) | Prevalence ratio for wheezing (95% CI) | Ratio of asthma to wheezing |
|---|---|---|---|---|
| Shaw *et al* (1990)[10] | New Zealand | 1.60 (1.02 to 2.51) | 1.50 (0.92 to 2.41) | 1.07 |
| Peat *et al* (1994)[12] | Australia | 1.88 (1.46 to 2.42) | 1.95 (1.68 to 2.29) | 0.96 |
| Burr *et al* (1989)[15] | United Kingdom | 2.17 (1.49 to 3.22) | 1.55 (1.21 to 2.01) | 1.40 |
| Rona *et al* (1995)[18] | United Kingdom | 2.70 (2.37 to 3.06) | 1.40 (1.30 to 1.51) | 1.93 |
| Hill *et al* (1989)[16] | United Kingdom | 1.48 (1.29 to 1.71) | 1.11 (1.01 to 1.23) | 1.33 |

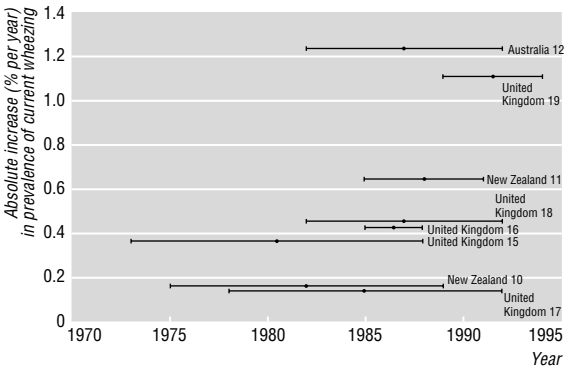


**Fig 2** Absolute yearly increases in prevalence of current wheezing in eight repeated cross sectional studies by country and time period. Bars indicate first and last survey years of each study. Points are midyears

populations we need to assess critically the informational content of the data.

### Asthma

A main concern is whether the content of the asthma diagnosis is changing. In 1983 a study from Newcastle showed a substantial underdiagnosis of asthma.[26] The increase in parent reported asthma observed during the 1980s may be a consequence of changes among physicians in making use of the asthma diagnosis and giving better information to parents.[16] Better treatment options with a focus on early introduction of drugs and a change in the criteria for applying the diagnosis to children[27] may also have increased the prevalence.[28] Changing criteria for asthma may also have relevance for the studies of conscripts in Israel,[21 22] in which physicians examined subjects with a wheezing history, and for the Taiwan study,[13] in which paediatricians revised the questionnaires. Physical examination for the determination of asthma adds a further layer of complexity, as the examination is subjective and the diagnosis of asthma may depend on the period in which the person is examined.

In addition to increased professional awareness, a public awareness bias may be present if allergies and asthma have been extensively discussed in public. After reviewing the many mechanisms that can influence an asthma diagnosis Anderson concluded that "the presence of a diagnosis of asthma is of little use epidemiologically."[29] On the basis of these considerations we cannot conclude from repeated studies that sought only the presence of asthma that asthma has increased.

### Wheezing

If we cannot trust the asthma diagnosis for time trend studies we are left with the increase in wheezing (table 2). The eight studies—from New Zealand, Australia, and the United Kingdom—showed variation in the yearly increase in prevalence of current wheezing from 0.14% in London[17] to 1.24% in two Australian towns.[12] A remaining question is whether the everyday meaning of the word wheezing has been constant over time. Do better educated parents more easily use this word for symptoms in their children? Is the tolerance of mild respiratory symptoms lower than it previously was? Have public health campaigns to increase the awareness of wheezing as a sign of asthma or media reports of increasing rates of asthma led to increased parental awareness of symptoms in their children? These questions cannot be answered from the studies reviewed. In the London study less disability in connection with wheezing was reported on the second occasion (1991).[17] This may be explained by an increase in the recognition and reporting of symptoms rather than by effects of treatment, which presumably should reduce disability and symptoms to the same degree.

### Lack of objective measures

Wheezing and other symptoms of obstruction are clinical expressions not easily captured by objective measurements in cross sectional studies. However, both bronchial hyperreactivity and positive skin prick test reactions are correlated with asthma,[13] though none of these measures provides a standard. But we should expect that the prevalence of these findings would increase in the general population of children if the prevalence of asthma really had increased.

Only two of the 16 studies included objective measurements on both occasions. In a study from Wales[15] peak expiratory flow rates were measured before (PEFR 1) and after (PEFR 2) six minutes of free running and the outcome analysed as $100 \times$(PEFR 2/PEFR 1). In both surveys (conducted in 1973 and 1988) the mean value was 96% (calculated from midpoint values in table 3). The prevalence of airway hyperresponsiveness induced by exercise (more than 15% decrease) was 6.7% (SE 0.9%) in 1973 and 7.7% (0.9%) in 1988. In an Australian study comparing schoolchildren in 1982 and 1992 there was no change in skin prick test positivity to five allergens.[12] The proportion of children who had a positive bronchial response to histamine challenge was twice as high in 1992 as in 1982. The type of spirometer used differed between the two occasions. An unknown point is whether the increased use of drugs might increase the response to histamine.

### Selection bias

Within each country the samples consisted of schoolchildren, students, or conscripts drawn from the

**Key messages**

- There is an increase in the reporting of wheezing illness in children
- The increase may be due to information bias
- There is a lack of objective measurements in population based samples to support claims for an increase in asthma
- The changing informational content complicates following the epidemiology of asthma

general population. There is a lack of repeated cross sectional studies of children below school age. Response rates are generally high. The important question is whether the repeated samples within studies are sufficiently comparable. We were careful to exclude studies that did not use the same geographic sampling frame (same schools or same regions). Nevertheless, the effects of selective migration between surveys cannot be controlled in detail and may influence some of the smaller studies based on samples of schoolchildren in cities. The studies based on conscripts[21 22 24] or on nationwide sampling[14 20] were more reliable in this respect. The studies were conducted in several countries representing large differences in geographic location and culture—namely, the United Kingdom, the United States, Australia and New Zealand, Taiwan, Sweden, Finland, and Israel. To complete the picture studies are needed from other countries, though it is unlikely that trends will be noticeably different. In our opinion, selection bias is unlikely to explain the observed trends.

**Conclusion**

The prevalence of asthma is difficult to follow over time owing to changes in diagnostic practice. The argument for an increase in obstructive lung disease among children rests on parental or self reports of symptoms in three countries (United Kingdom, New Zealand, and Australia) and finding an increased prevalence of bronchial hyperresponsiveness to a histamine challenge in one study. Information bias may explain the trends. It is encouraging that new epidemiological studies are under way with standardised questions on severity and objective measurements.[30] Until such studies have been performed on more than one occasion in the same population we believe that the evidence for an increasing trend in obstructive lung disease among children and young adults is weak.

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*Endpiece*

**Paradigms and "normal science"**

Mopping-up operations are what engage most scientists throughout their careers. They constitute what I am here calling normal science. Closely examined, whether historically or in the contemporary laboratory, that enterprise seems an attempt to force nature into the preformed and relatively inflexible box that the paradigm supplies. Nor do scientists normally aim to invent new theories . . . normal scientific research is directed to the articulation of those phenomena and theories that the paradigm already supplies.

Thomas S Kuhn, *The Structure of Scientific Revolutions* (1962)

# Treatment of herpes simplex gingivostomatitis with aciclovir in children: a randomised double blind placebo controlled study

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## Abstract

**Objectives:** To examine the efficacy of aciclovir suspension for treating herpetic gingivostomatitis in young children.
**Design:** Randomised double blind placebo controlled study.
**Setting:** Day care unit of a tertiary paediatric hospital.
**Subjects:** 72 children aged 1-6 years with clinical manifestations of gingivostomatitis lasting less than 72 hours; 61 children with cultures positive for herpes simplex virus finished the study.
**Main outcome measures:** Duration of oral lesions, fever, eating and drinking difficulties, and viral shedding.
**Intervention:** Aciclovir suspension 15 mg/kg five times a day for seven days, or placebo.
**Results:** Children receiving aciclovir had oral lesions for a shorter period than children receiving placebo (median 4 *v* 10 days (difference 6 days, 95% confidence interval 4.0 to 8.0)) and earlier disappearance of the following signs and symptoms: fever (1 *v* 3 days (2 days, 0.8 to 3.2)); extraoral lesions (lesions around the mouth but outside the oral cavity) (0 *v* 5.5 days (5.5 days, 1.3 to 4.7)); eating difficulties (4 *v* 7 days (3 days, 1.31 to 4.69)); and drinking difficulties (3 *v* 6 days (3 days, 1.1 to 4.9)). Viral shedding was significantly shorter in the group treated with aciclovir (1 *v* 5 days (4 days, 2.9 to 5.1)).
**Conclusions:** Oral aciclovir treatment for herpetic gingivostomatitis, started within the first three days of onset, shortens the duration of all clinical manifestations and the infectivity of affected children. Further studies are needed to evaluate the ideal dose and length of treatment.

## Introduction

Herpetic gingivostomatitis is the most common clinical manifestation of primary herpes simplex virus infection in young children. Although it is a self limiting disease, the general course is 10-14 days, and the children experience extreme discomfort and refuse to eat. If they also refuse to drink they often have to be admitted to hospital for rehydration.

Parenteral aciclovir has been shown to be effective in herpes simplex virus infections such as encephalitis,[1] primary genital herpes,[2] and herpes neonatorum.[3] Oral aciclovir has been used successfully to treat genital herpes[4 5] and recurrent herpes labialis.[6] No study has shown definitively, however, that oral aciclovir is effective for primary herpes gingivostomatitis. Encouraging results have been reported in a few open studies,[7 8] a small controlled study,[9] and a prophylactic trial during an outbreak in a closed community.[10]

This randomised, double blind, placebo controlled study was designed to examine the efficacy of oral aciclovir suspension for treating herpetic gingivostomatitis in young children.

## Subjects and methods

### Subjects

All children aged 1-6 years of age with clinical manifestation of gingivostomatitis lasting less than 72 hours were identified by their primary pediatrician and referred to the paediatric day care unit of Hasharon Hospital, Petah Tiqva, Israel. Children seen in the emergency room of Hasharon Hospital and the Schneider Children's Medical Centre were also recruited.

After a swab from the oral lesions for viral cultures and blood for serological tests for herpes simplex virus were obtained, the children were assigned the next available study number by using a randomised number table with a block size of eight. The same numbers were on the study treatments—aciclovir suspension or placebo suspension. The placebo bottles were identical to the aciclovir bottles, and the suspension looked exactly the same with a similar smell. The aciclovir was given in a dose of 15 mg/kg (0.375 ml/kg), five times a day (up to a maximum of 200 mg per dose) for a period of seven days, and the placebo was given in the same volume, five times a day.

Written informed consent was obtained from the parents, and the study was approved by the hospital's ethics committee.

### Assessment

On enrolment (day 0), a medical history was taken and physical examination performed. On clinical evaluation, fever, severity of the oral lesions, presence of extraoral skin lesions (lesions around the mouth but outside the oral cavity), drooling, and drinking and eating difficulties were noted. The oral lesions were categorised as mild (up to 10 lesions on the tongue or oral mucous membrane), moderate (11 to 20 lesions with swelling of the gums), or severe (more than 20 tongue or oral lesions and gum lesions). Drinking and eating abilities were categorised as normal, less than normal, and total inability to drink or eat.

The clinical examination was repeated on days 3, 6, and 8, the day after ending the treatment, and thereafter every two to three days if symptoms persisted. The parents recorded the child's symptoms, and the rectal temperature was measured daily until a normal reading ($<38.0$°C) was obtained for more than 24 hours. Compliance was measured by the volume of suspension left in the bottle. A single investigator (JA) carried out the follow up evaluation of all the children.

### Laboratory investigations

On day 0, in addition to the culture and serological tests, a full blood count was performed. The viral

cultures were repeated at each visit until the complete disappearance of all oral or extraoral lesions. A second sample for serological testing for herpes simplex virus was obtained between day 12 and day 16.

*Culture of herpes simplex virus*—The culture swabs were placed into 2 ml of transport medium,[11] and the specimens were either sent immediately on ice to the Central Virology Laboratory, Tel Hashomer, or kept refrigerated overnight and sent the next day. The herpes simplex virus was isolated as described previously.[12]

*Serotyping of herpes simplex virus with monoclonal antibodies*—All isolates of herpes simplex virus were typed by fluorescence conjugate monoclonal antibodies (Syva Microtak HSV-1, HSV-2; Palo Alto, CA), according to the manufacturer's instructions.[12]

*Serology assays*—An indirect immunofluorescence antibody test was performed as described previously.[13]

### Statistical analysis

The sample size was calculated on the assumption that the clinical symptoms of herpes simplex virus gingivostomatitis may last 5-15 days with a standard deviation of five days. On the basis of these data, we estimated that a sample size of 60 children with proved herpes simplex virus would be needed to detect a difference of 2.5-3.0 days between the treatment groups with a power of 0.80 and a significance level of 0.05. The times of disappearance of symptoms (mouth lesions, fever, external lesions, drooling, and eating and drinking difficulties) were compared by the Mann-Whitney non-parametric test. The severity scores of eating and drinking difficulties were compared by the $\chi^2$ test.

The *t* test was applied to compare the groups with respect to the continuous variables—that is, the difference in maximal temperature, the laboratory results (haemoglobin, polymorphonuclear cells, and lymphocytes), and the number of days to the last positive culture and to the first negative culture. Finally, Fisher's exact test was used to determine differences in the level of compliance and admission between the groups. Only children with laboratory evidence of herpes simplex virus infection (positive culture or serological result) were included in the statistical analysis for efficacy outcome, according to the protocol.

## Results

Altogether, 72 children were enrolled between December 1993 and February 1995. Thirty six children were randomly allocated to receive aciclovir and 36 to receive the placebo. Ten children whose viral cultures were negative for herpes simplex virus and whose serological results remained negative during convalescence were excluded from the clinical evaluation, as was one child whose parents refused to continue with the follow up after day 2. Thus, the final study population comprised 61 children with positive cultures for herpes simplex virus; 31 children were in the group receiving aciclovir and 30 were in the placebo group.

On enrolment both groups were similar regarding demographic variables and severity of clinical symptomatology (table 1). Two children in the aciclovir group and three in the placebo group were admitted for rehydration at enrolment.

**Table 1** Demographic, clinical, and haematological variables at admission in 61 children in ambulatory care unit of a tertiary paediatric hospital

| | Treatment group | |
|---|---|---|
| | **Aciclovir** | **Placebo** |
| No of patients | 31 | 30 |
| Age (SD; range) (months) | 33.1 (23; 10-82) | 35.9 (21; 12-77) |
| Mean (SD; range) weight (kg) | 14.6 (6; 8.4-30.0) | 14.6 (4; 9.7-26.0) |
| Male:female | 14:17 | 16:14 |
| No of days' duration (SD) of oral lesions | 2.0 (0.8) | 2.1 (0.9) |
| No of extraoral lesions | 10 | 8 |
| No of patients admitted to hospital | 2 | 3 |
| Severity of oral lesions*: | | |
| Mild | 11 | 7 |
| Moderate | 16 | 17 |
| Severe | 4 | 6 |
| **Feeding and drinking abilities** | | |
| Eating: | | |
| Normal | 0 | 0 |
| Less than normal | 12 | 12 |
| Unable to eat | 19 | 18 |
| Drinking: | | |
| Normal | 3 | 1 |
| Less than normal | 26 | 27 |
| Unable | 2 | 2 |
| Hemoglobin (SD) (g/l) | 111 (9) | 109 (11) |
| White blood cells (SD) ($10^6$ cells/l) | 9883 (2188) | 9971 (5020) |
| % (SD) Lymphocytes | 44 (15) | 36 (13) |

*Mild: up to 10 lesions on the tongue or oral mucous membrane; moderate: 11 to 20 lesions with swelling of the gums; severe: more than 20 tongue or oral lesions and gum lesions.

**Table 2** Median (range) duration (in days) of clinical variables in 61 children with confirmed herpes simplex virus gingivostomatitis

| | Treatment group | | |
|---|---|---|---|
| **Clinical variable** | **Aciclovir (n=31)** | **Placebo (n=30)** | **Difference in medians (95% CI)** |
| Oral lesions | 4 (2-12) | 10 (3-15) | 6 (4.0 to 8.0) |
| Fever | 1 (1-3) | 3 (1-6) | 2 (0.8 to 3.2) |
| Extraoral lesions | 0 (0-8) | 5.5 (0-16) | 5.5 (1.0 to 10.0) |
| Drooling | 2 (0-8) | 5.5 (0-12) | 3.5 (2.0 to 5.0) |
| Eating difficulties | 4 (1-12) | 7 (3-14) | 3 (1.3 to 4.7) |
| Drinking difficulties | 3 (1-8) | 6 (1-11) | 3 (1.1 to 4.9) |
| Viral shedding | 1 (1-3) | 5 (1-10) | 4 (2.9 to 5.1) |

The children in the aciclovir group had significantly more blood lymphocytes than those in the placebo group (table 1). The other haematological variables were similar.

### Efficacy outcome

*Oral lesions*—The oral lesions persisted for a significantly shorter time in the children receiving aciclovir than in those receiving placebo (median 4 (range 2-12) days *v* 10 (3-15) (table 2)). At the end of treatment on day 8, two out of 31 children in the aciclovir group had oral lesions compared with 21 out of 30 in the placebo group.

*Fever*—The fever disappeared significantly earlier in the children in the aciclovir group than in those in the placebo group (median 1 day *v* 3 days (table 2).

*Extraoral lesions*—On day 0 about one third of the children in each group had extraoral herpetic lesions

**Table 3** Median (range) duration (in days) of clinical variables of all enrolled children (n=72)

| Clinical variable | Treatment group: Aciclovir (n=36) | Treatment group: Placebo (n=35) | Difference in medians (95% CI) |
|---|---|---|---|
| Oral lesions | 4 (2-12) | 9 (3-15) | 5 (2.4 to 7.6) |
| Fever | 1 (0-3) | 2 (0-6) | 1 (0.0 to 2.0) |
| Extraoral lesions | 0 (0-8) | 3 (0-16) | 3 (1.4 to 4.6) |
| Drooling | 2 (0-8) | 5 (0-12) | 3 (1.4 to 4.5) |
| Eating difficulties | 4 (1-12) | 7 (0-14) | 3 (1.2 to 4.8) |
| Drinking difficulties | 3 (1-8) | 5 (1-11) | 2 (0.3 to 3.7) |
| Viral shedding | 1 (0-3) | 5 (0-10) | 4 (2.7 to 5.3) |

(table 1). Children in the aciclovir group did not develop new lesions after treatment had been started. Twelve of those in the placebo group, however, continued to develop extraoral lesions after the treatment had been started. The duration of the lesion was significantly shorter in the aciclovir group (median 0.0 *v* 5.5 days (table 2)).

*Eating and drinking ability*—On enrolment all the children had eating and drinking difficulties. On day 8 of the treatment, in the aciclovir group two children had eating difficulties and one child had drinking difficulties, compared with 14 and 9 children respectively in the placebo group. The median duration of the eating difficulties was 4 *v* 7 days respectively and of drinking difficulties was 3 *v* 6 days respectively (table 2).

*Duration of clinical variables*—Table 3 represents the clinical data of all the children randomised in the study except the one child who left the study on day 2. Ten of the 71 children showed no evidence of herpes simplex virus infection. In the intention to treat analysis, the duration of all measured clinical variables was still significantly shorter in the aciclovir group than in the placebo group (table 3).

*Hospital admission*—Five children were admitted before inclusion in the study (table 1). Among the children not admitted, none treated with aciclovir was admitted after treatment was started, while three children in the placebo group were admitted for two to three days for rehydration (P = 0.11).

*Recurrences*—Telephone screening of the enrolled children 16 months after the start of the study showed only one case of herpes labialis (in a child in the placebo group).

*Viral cultures*—All the cultures (positive for herpes simplex virus in all the children included in the study) were identified as type 1. The cultures were obtained every two to three days, so if a child had a positive culture on day 0 and on day 3, we assumed that he or she was positive also on days 1 and 2. According to this evaluation, the children in the aciclovir group had a significantly shorter period of positive viral culture than those in the placebo group (median (range 1-3) 1 *v* 5 (1-10) days) respectively (difference 4 days, 95% confidence interval 2.9 to 5.1) (table 2).

*Serological examination*—Serology samples were taken during the acute and convalescence phases of the infection were available for 41 children. In those with culture negative for herpes simplex virus (10 cases), the serological findings for the convalescence samples were negative. Of those included in the efficacy calculation, 18 were from the aciclovir group and 13 from the placebo group. No differences between groups in seroconversion or maximal titres of immunofluorescence antibody were observed. All children had seroconversion with titres of $>64$.

*Compliance*—Compliance was good in both groups: 29 children in the aciclovir group and 24 in the placebo group received $>80\%$ of the prescribed treatment, and the rest used 50-80% (P = 0.117).

*Side effects*—No significant side effects were recorded in either group. Two children in each group had mild gastrointestinal symptoms that resolved spontaneously after 24 to 48 hours without a change in the study treatment.

## Discussion

Treatment with oral aciclovir suspension—started during the first three days of the appearance of herpetic gingivostomatitis and continued for seven days—was shown to be significantly more effective than placebo in reducing the severity of the clinical symptoms and shortening the period of infectivity as a result of viral shedding. The beneficial effect of aciclovir was evident in all clinical variables evaluated, the healing rate of the oral and extraoral lesions, duration of the fever, and the duration of the eating and drinking difficulties. In an intention to treat analysis of all enrolled children, including those without proved herpes simplex virus infection, the difference between the treatment groups remained highly significant (table 3). No child in the aciclovir group was admitted after treatment had been started, compared with three children in the placebo group who were admitted for rehydration.

The beneficial effect of aciclovir treatment has been previously reported in an open study.[7] The study showed that in children with herpetic gingivostomatitis who were treated with aciclovir, fever disappeared after the third day of treatment in all cases, concomitant with marked improvement in the oral lesions. Of the 33 children, only about 10% had oral or extraoral lesions after six days of treatment.

Herpes gingivostomatitis is a contagious disease, especially among children in closed communities or day care centres.[14,15] Data regarding intrafamilial transmission are unclear.

In young children herpes simplex virus is transmitted primarily by contact with infected oral secretions. In the children treated with aciclovir, the period of viral shedding was significantly shorter than in those receiving placebo. After three days of aciclovir treatment all viral cultures became negative, compared with almost 50% positive cultures on day 6 in the placebo group, probably indicating a decrease in the infectivity of the treated children.

Recurrences of gingivostomatitis are unusual in normal hosts and are most probably related to immunity after infections. One important question is the effect of aciclovir treatment on long term immunity against herpes simplex virus. The serological data in this study, although available for only half the children, showed no difference between the aciclovir and placebo groups in the humoral immune response to the virus. The influence of the treatment on local recurrences needs long term follow up.

Concern has been expressed over the possible selection of resistant strains once aciclovir is being used

**Key messages**

- Herpetic gingivostomatitis is the most common clinical manifestation of primary herpes simplex virus infection in young children
- The efficacy of oral aciclovir suspension was studied in a double blind placebo controlled study
- All clinical symptoms and viral shedding were shorter in children receiving aciclovir than in those receiving placebo
- Aciclovir was highly effective in treating children with herpetic gingivostomatitis

for such relatively common disorders as herpetic gingivostomatitis. Most clinical isolates resistant to aciclovir have been recovered from immunocompromised patients receiving multiple treatment courses. A seven day treatment of aciclovir in normal children is unlikely therefore to create a problem. Aciclovir has been used to prevent recurrent genital herpes for more than six years, and no resistant strains have been isolated.[16]

The clinical manifestation of herpetic gingivostomatitis varies from a mild illness to a severe course with admission to hospital. In the placebo group (n = 30), which represented the natural course of herpetic gingivostomatitis, oral lesions were found in 25 children for seven days or more, and eating and drinking difficulties in 16 (data not shown). During this period, the sick children were unable to attend day care or kindergarten. Although this study did not attempt to address the economic issue of aciclovir treatment in gingivostomatitis, the significant reduction in the duration of illness and the prevention of admission are likely to allow children and parents to return to their normal life earlier, a benefit that may balance the price of the treatment.

Conflict of interest: None.

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# Unsupervised surgical training: questionnaire study

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Most surgeons have anecdotal awareness of trainees carrying out, unsupervised, operations which they have never previously performed. This is the first formal attempt to quantify this variant of surgical "training."

## Methods and results

Questionnaires were sent to 451 trainee surgeons and young consultants in the United Kingdom. Replies were received from 276 (61%): 144/230 (63%) members of the Association of Surgeons in Training and 132/221 (60%) otolaryngologists from the Association of Otolaryngologists in Training and the Young Consultant Otolaryngologists Head and Neck Surgeons.

Respondents were asked to indicate whether they had ever undertaken a surgical procedure for the first time "without your trainer being present in the theatre"; to specify any such procedure; to "asterisk any where you can recall your senior not being present in the hospital at the time"; and to select the statement that most closely reflected their attitude to this practice. Consultants were asked to indicate the number of different procedures they had performed for the first time since appointment.

Experience of first time unsupervised procedures was significantly commoner among general than otolaryngological surgeons (86% *v* 66%; $\chi^2 = 14.7$, $P < 0.001$) (table 1). Senior house officers undertook submandibular gland excision, femoral hernia, Mayo repair, testicular torsion, partial gastrectomy,

**Table 1** Procedures performed, unsupervised, for the first time by trainee surgeons and young consultants

| | Association of Surgeons in Training | | | | Otolaryngologists* | | | |
|---|---|---|---|---|---|---|---|---|
| | Senior house officer or registrar | Senior registrar | Consultant | All grades (%) | Senior registrar | Consultant | All grades (%) | Total (%) |
| Respondents | 68 | 59 | 17 | 144 | 48 | 84 | 132 | 276 |
| No performed first time unsupervised | | | | | | | | |
| 0 | 12 | 8 | 0 | 20 (14) | 20 | 25 | 45 (34) | 65 (24) |
| 1 | 6 | 2 | 3 | 11 (8) | 5 | 11 | 16 (12) | 27 (10) |
| 2 | 14 | 6 | 4 | 23 (16) | 10 | 26 | 36 (27) | 59 (21) |
| 3 | 12 | 17 | 3 | 31 (22) | 7 | 7 | 14 (11) | 46 (17) |
| 4 | 12 | 5 | 1 | 17 (12) | 4 | 5 | 8 (6) | 26 (9) |
| 5-11 | 6 | 5 | 0 | 11 (8) | 5 | 3 | 8 (6) | 19 (7) |
| Too many to list | 6 | 16 | 6 | 27 (19) | 0 | 4 | 4 (3) | 32 (12) |
| Attitude to performing first time unsupervised†: | (n=56) | (n=31) | (n=17) | (n=124) | (n=29) | (n=59) | (n=88) | (n=212) |
| Beneficial to confront new surgical situation | 14 | 15 | 1 | 30 (24) | 7 | 25 | 32 (36) | 62 (29) |
| Results technically ok; poor training | 31 | 37 | 11 | 79 (64) | 18 | 27 | 45 (51) | 124 (58) |
| Unsatisfactory results and training | 6 | 13 | 3 | 22 (18) | 5 | 7 | 12 (14) | 34 (16) |
| Other | 3 | 1 | 1 | 5 (4) | 3 | 5 | 8 (9) | 13 (6) |

*Results exclude prespecialty general training.
†Some respondents gave more than one reply.

splenectomy, and cholecystectomy with the "senior" absent from the hospital. Registrars' unsupervised hepatobiliary procedures included triple bypass for pancreatic carcinoma, common bile duct exploration, choledochoduodenostomy, "hot" cholecystectomy, laparotomy for liver trauma, and a Whipple's procedure. Registrars also reported 20 large bowel resections, six aneurysm repairs, a renal transplant, and a mesenteric embolectomy; senior registrars' procedures included axillary clearance, elective aneurysm surgery, oesophagectomy, distal pancreatectomy, mastectomy, open prostatectomy, horseshoe nephrectomy, and gastroplasty for morbid obesity. Otolaryngologists performed 34 major head and neck procedures (laryngectomy, pharyngolaryngectomy, parotidectomy, thyroidectomy, radical neck dissection, hemiglossectomy, free tissue transfer), 27 major nose and sinus procedures (including 3 external rhinoplasties, 3 lateral rhinotomies, 2 total maxillectomies, 5 orbital decompressions, and 14 arterial ligations for epistaxis), and 34 major ear procedures.

Of 17 general surgical consultant respondents, five had performed a procedure not seen during training and seven had performed procedures only assisted at in training. Most reported only one such operation, but one of the group included "all majors" in this category. The greater the interval since qualification in the 84 otolaryngological consultants (1981 to 1994), the greater the number of first time consultant procedures. Sixty one (73%) had performed procedures not seen during training (45% had performed 1-4; 11% 5-9; 9% 10-19; and 7% 20-50 procedures); 41 had performed operations only observed as trainees.

## Comment

The results are based on the responses of a large sample, collected anonymously; they are in line with reports that two thirds of all procedures by surgical trainees are unassisted.[1,2]

Many first time unsupervised procedures are undertaken as out of hours emergencies (one reason for the smaller numbers in otolaryngology). Most responsible trainers (and members of the public) will agree with the view of the trainees that unsupervised first time surgery is not ideal training. Preservation of training status for a unit should require returning a much more complete dataset than is currently available for audit of training.[1] Surgical log books should include a more formal evaluation of procedures that appear for the first time in the absence of a senior assistant.

As the specialist registrar grade is introduced, assessors must be aware of the risk of excessive "first time" surgery for young consultants. Some of this experience in otolaryngology was the result of surgical advance—33 procedures were functional endoscopic sinus surgery, which is new in Britain. Conversely, the 38 head and neck procedures that respondents performed but had never previously seen supports the urgent need for specialist head and neck training modules.

I thank the organisers and members of the Association of Surgeons in Training, the Young Consultant Otolaryngologists Head and Neck Surgeons, and the Association of Otolaryngologists in Training for their cooperation and their honesty.

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*Endpiece*

### Dr Johnson on the impermanence of language

Words are the daughters of earth, and things are the sons of heaven. Language is only the instrument of science, and words are but the signs of ideas. I wish, however, that the instrument might be less apt to decay, and that signs might be permanent, like the things which they denote.

Preface to Johnson's *Dictionary of the English Language* (1775)

# Drug points

## Ocular damage associated with proton pump inhibitors

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Ocular damage has been associated with the intravenous use of high doses of omeprazole. A pharmacoepidemiological study recently found no association between omeprazole and impaired vision in a population of about 95 000.[1] However, our monitoring unit for serious adverse drug reactions in Bremen has registered nine cases of impaired vision associated with the use of omeprazole, but none with other antiulcer drugs such as $H_2$ receptor antagonists (table 1). Six cases were funduscopically confirmed irreversible anterior ischaemic optic neuropathy. Two cases (6 and 7) occurred when there were no known risk factors for anterior ischaemic optic neuropathy, oral omeprazole had been taken alone, and no other drugs had been taken for at least four weeks before the event.

In August 1993 a 55 year old teacher was treated for gastric ulcer with oral omeprazole, 40 mg daily during the first week, followed by 20 mg daily for five weeks. She noted that her vision was impaired on the second day of treatment, but the symptoms spontaneously disappeared a few days later. At the end of the treatment period she again noted impaired vision, which persisted. Funduscopic examination showed papillary oedema and papillitis in the right eye, which progressed to anterior ischaemic optic neuropathy with persistent visual field defects during the following weeks. Angiographic and serological investigations did not show any underlying disease. No other lesions of central nervous system white matter were found on computed tomography and magnetic resonance imaging, arguing against a diagnosis of multiple sclerosis.

A 48 year old man with recurrent duodenal ulcers first received treatment with omeprazole for six weeks (orally 20 mg daily) in April 1993. When his ulcers recurred in the autumn of that year, the same treatment regimen with omeprazole was repeated. Within one week he noted impaired vision and ocular pain in his left eye. Anterior ischaemic optic neuropathy was confirmed funduscopically, with irreversible visual impairment (vision 0.6, temporal visual field defect). Again, thorough neurological and laboratory examinations did not find any disease of other origin and computed tomography did not show any additional neurological lesions suggestive of multiple sclerosis.

Recently, a similar case was reported with oral pantoprazole.[2] Preclinical studies with lansoprazole have also shown irreversible ischaemic optic nerve damage in beagle dogs. These observations suggest a common mechanism, possibly depending on the inhibition of ATPases. Proton pump inhibitors seem not to act specifically on potassium-hydrogen ATPases in gastric mucosa. Omeprazole inhibits the secretion of cerebrospinal fluid in rats by decreasing ATPase activity. Reduction in intracellular pH by omeprazole induced blockade of potassium-hydrogen ATPase results in decreased renal function, and renal failure as well as interstitial nephritis have been observed with omeprazole.[3] Potassium-hydrogen ATPase is present in vascular smooth muscle cells,[4] and reduction in intracellular pH causes vasoconstriction.[5] Chest pain or angina and raised blood pressure are mentioned as adverse reactions in the United States data sheet on omeprazole. Anterior ischaemic optic neuropathy may, therefore, be caused by proton pump inhibitors blocking potassium-hydrogen ATPase, possibly inducing vasoconstriction and ischaemia in end arteries such as the retinal artery.

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**Table 1** Cases of ocular damage after omeprazole reported to monitoring unit in Bremen, Germany

| Case No | Age (years) sex | Underlying disease | Omeprazole daily regimen | Time to event | No of other drugs | Adverse drug reaction; outcome |
|---|---|---|---|---|---|---|
| 1 | 59 M | Pyloric stenosis, chronic pancreatitis | 80 mg intravenously | 3 Days | 3 | Anterior ischaemic optic neuropathy; blind |
| 2 | 51 M | Gastric haemorrhage | 40 mg intravenously (4 days); 20 mg orally (3 days) | 7 Days | 3 | Anterior ischaemic optic neuropathy; blind |
| 3 | 33 F | Erosive gastritis, breast cancer | 80 mg intravenously | 3 Days | 5 | Blurred vision; died (death not related to drug) |
| 4 | 29 M | Major burns | 40 mg intravenously | 19 Days | Multiple | Anterior ischaemic optic neuropathy; blind |
| 5 | 25 M | Major burns | 40-120 mg intravenously | 24 Days | Multiple | Anterior ischaemic optic neuropathy; blind |
| 6 | 48 M | Recurrent duodenal ulcer | 20 mg orally | 7 Days | 0 | Anterior ischaemic optic neuropathy in left eye, visual field defect; reduced visual acuity (irreversible) |
| 7 | 55 F | Gastric ulcer | 40 mg orally (1 week); 20 mg orally (5 weeks) | 6 Weeks | 0 | Anterior ischaemic optic neuropathy in right eye, visual field defect; reduced visual acuity (irreversible) |
| 8 | 62 M | Pancreas insufficiency, diabetes | 20 mg orally | 7 Months | 3 | Blurred vision; reversible (on withdrawal) |
| 9 | 70 F | Gastroesophageal reflux | 20 mg orally (3 months); 40 mg orally (3 months); 60 mg orally (8 days) | 8 Days | 1 | Blurred vision, reduced visual acuity, ischaemic retinopathy; reversible (on withdrawal) |