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RESEARCH

Combining insulin with metformin or an insulin secretagogue in non-obese patients with type 2 diabetes: 12 month, randomised, double blind trial

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Cite this as: *BMJ* 2009;339:b4324
doi: 10.1136/bmj.b4324

ABSTRACT

Objectives To study the effect of insulin treatment in combination with metformin or an insulin secretagogue, repaglinide, on glycaemic regulation in non-obese patients with type 2 diabetes.

Design Randomised, double blind, double dummy, parallel trial.

Setting Secondary care in Denmark between 2003 and 2006.

Participants Non-obese patients (BMI ≤27) with preserved beta cell function.

Interventions After a four month run-in period with repaglinide plus metformin combination therapy, patients with a glycated haemoglobin (HbA_{1c}) concentration of 6.5% or more were randomised to repaglinide 6 mg or metformin 2000 mg. All patients also received biphasic insulin aspart 70/30 (30% soluble insulin aspart and 70% intermediate acting insulin aspart) 6 units once a day before dinner for 12 months. Insulin dose was adjusted aiming for a fasting plasma glucose concentration of 4.0-6.0 mmol/l. The target of HbA_{1c} concentration was less than 6.5%. Treatment was intensified to two or three insulin injections a day if glycaemic targets were not reached.

Main outcome measure HbA_{1c} concentration.

Results Of the 459 patients who were eligible, 102 were randomised, and 97 completed the trial. Patients had had type 2 diabetes for approximately 10 years. At the end of treatment, HbA_{1c} concentration was reduced by a similar amount in the two treatment groups (insulin plus metformin: mean (standard deviation) HbA_{1c} 8.15% (1.32) *v* 6.72% (0.66); insulin plus repaglinide: 8.07% (1.49) *v* 6.90% (0.68); P=0.177). Total daily insulin dose and risk of hypoglycaemia were also similar in the two treatment groups. Weight gain was less with metformin plus biphasic insulin aspart 70/30 than with repaglinide plus biphasic insulin aspart 70/30 (difference in mean body weight between treatments −2.51 kg, 95% confidence interval −4.07 to −0.95).

Conclusions In non-obese patients with type 2 diabetes and poor glycaemic regulation on oral hypoglycaemic agents, overall glycaemic regulation with insulin in combination with metformin was equivalent to that with insulin plus repaglinide. Weight gain seemed less with insulin plus metformin than with insulin plus repaglinide.

Trial registration NCT00118963

WHAT IS ALREADY KNOWN ON THIS TOPIC

Use of metformin in non-obese patients with type 2 diabetes is controversial

There is insufficient evidence to support the use of metformin or an insulin secretagogue in addition to insulin therapy in non-obese patients with type 2 diabetes

WHAT THIS STUDY ADDS

In non-obese patients with type 2 diabetes, biphasic insulin aspart 70/30 plus metformin and biphasic insulin aspart 70/30 plus the insulin secretagogue repaglinide are both safe and effective means of glycaemic regulation

Biphasic insulin aspart 70/30 plus metformin and biphasic insulin aspart 70/30 plus repaglinide provide equal glycaemic control and have an equal risk of hypoglycaemia

Weight gain appeared less with insulin plus metformin than with insulin plus repaglinide

INTRODUCTION

Metformin is an oral hypoglycaemic agent that targets insulin resistance. In obese patients with type 2 diabetes metformin is considered to have cardioprotective effects and is the preferred glucose lowering drug to use as monotherapy or in combination with insulin.[1-6] In contrast, the use of metformin in non-obese patients with type 2 diabetes is controversial.[1 3 4 7] It is not known whether insulin plus metformin has a similar glucose lowering potency in these patients as an "insulin providing" combination regimen of insulin plus an insulin secretagogue.

Repaglinide is a meglitinide analogue: a short acting insulin secretagogue with a similar glucose lowering effect, lower risk of hypoglycaemia, and better effect on cardiovascular disease surrogate markers than other insulin secretagogues such as glibenclamide. It has been suggested to have similar cardioprotective effects to metformin.[8]

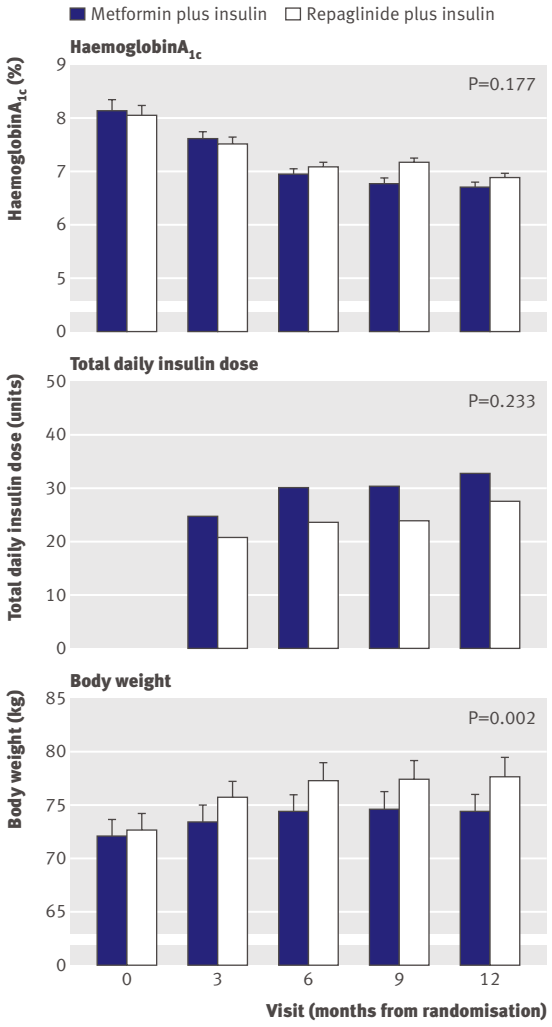
We tested the hypothesis that combination therapy for one year with metformin plus biphasic insulin aspart 70/30 has equal glucose lowering efficacy to the insulin secretagogue repaglinide plus biphasic insulin aspart 70/30 in non-obese patients with type 2 diabetes who

This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2009;339:b4324

have poor glycaemic control on combination therapy of oral hypoglycaemic agents.

METHODS

The study was an investigator initiated, single centre, prospective, randomised, double blind, double dummy, parallel trial of metformin plus biphasic insulin aspart 70/30 compared with repaglinide plus biphasic insulin aspart 70/30 (hereafter termed "insulin" in the Methods and Results sections). Patients were enrolled between February 2003 and September 2004. A targeted approach using electronic patient records as search objects for eligibility was used among approximately 5500 patients, about 40% of whom had type 2 diabetes. All potentially eligible non-obese patients with type 2 diabetes (n=459) were invited to participate, 155 of whom consented and entered the screening phase. A total of 133 patients with a BMI of 27 or less (corresponding to the criterion for non-obesity criteria used in the UK Prospective Diabetes Study[1]) and an initial HbA_{1c} concentration of 6.5% or more were selected for inclusion. See bmj.com.



Metabolic variables during 12 months of treatment with metformin plus insulin or repaglinide plus insulin. Data represent the number of patients with available data at each visit (that is, excluding dropouts), whereas P values represent tests with last observation carried forward

After the screening period, patients entered a four month run-in period. All patients received combination therapy with metformin (1000 mg twice a day) plus repaglinide (2 mg three times a day) and stopped prior glucose lowering treatments. Doses were adjusted by forced titration to reach maximum tolerated doses.

At the end of the run-in period, 102 patients were randomly allocated to receive 12 months' combination therapy with either repaglinide, insulin, and placebo metformin, or metformin, insulin, and placebo repaglinide. Active and placebo tablets were identical in appearance, taste, and smell.

The starting dose of insulin was six units injected before dinner. Patients self adjusted insulin dose every third day according to a predefined algorithm, aiming for a fasting plasma glucose concentration of 4.0-6.0 mmol/l. The target of HbA_{1c} concentration was less than 6.5%. Patients who were not receiving concomitant treatment with aspirin or a statin started them. They were asked not to make any lifestyle modifications during the trial.

The starting dose of insulin was six units injected before dinner. Patients self adjusted insulin dose every third day according to a predefined algorithm, aiming for a fasting plasma glucose concentration of 4.0-6.0 mmol/l. The target HbA_{1c} concentration was less than 6.5%. Patients who were not receiving concomitant treatment with aspirin or a statin initiated such treatments.

Outcome measures

The primary outcome was HbA_{1c} concentration (normal limits: 4.1-6.4%). Secondary outcomes were insulin doses, self monitored plasma glucose, measures of adiposity, and adverse events. Outcomes were assessed at enrolment (screening period: −4.5 and −4 months visits), at baseline (0 month visit), and on the last day of treatment (12 month visit). Clinical status was assessed at −2, 3, 6, and 9 months. Follow-up ended in February 2006.

Statistics

For the primary outcome, the randomised population was analysed on an intention to treat basis, with last observation carried forward for missing values at the end of treatment. Insulin dose was analysed in a similar way, whereas other secondary outcomes were analysed without last observation carried forward. Differences in treatment effects between the randomised interventions were evaluated as change from baseline. Self monitored plasma glucose measurements included those measurements made during the last two weeks before study visits.

An analysis of covariance model was developed for the primary outcome, with patient as the random effect, treatment (metformin plus insulin or repaglinide plus insulin) as the fixed effect, and baseline levels as the covariate. The secondary outcomes, having only one measurement per visit, were analysed similarly but without a random effect. Hypoglycaemia was analysed by a regression model.

From our power calculation we needed to enrol 100 subjects which allowed for 16 dropouts. See bmj.com for full statistical details.

RESULTS

Patient characteristics

A total of 102 patients were randomly allocated to either study arm, 101 were included in the intention to treat analysis and, after dropouts, 51 patients (98.1%) completed the 12 month treatment period with metformin plus insulin and 46 patients (93.9%) completed repaglinide plus insulin. Those patients who were invited but declined to participate were on average about three years older and had diabetes for two years longer than patients who agreed to participate (P=0.001 and P=0.002, respectively). In contrast, BMI and HbA_{1c} concentration did not differ significantly between these groups.

All patients were white and aged approximately 60 years. About two thirds were male and the median duration of diabetes was 8-12 years. The mean BMI was 24-25 and, before enrolment, about 80% of patients used oral hypoglycaemic agents and about 40% used insulin (about 20% of patients used both). Mean HbA_{1c} concentration at enrolment was 7.8%. See bmj.com.

Main outcomes

The mean HbA_{1c} concentration decreased by approximately 1% during the initial six months of treatment in both treatment groups and stabilised thereafter. At the end of treatment, both treatment groups achieved a mean level of HbA_{1c} below 7.0%, with no significant difference between treatments (P=0.177; figure).

The number of patients who achieved an HbA_{1c} concentration of less than 6.5% at the end of treatment was not significantly different between treatment groups (P=0.169). The glycaemic response to treatment did not seem to differ according to previous insulin treatment or known duration of diabetes. In those patients who had negative glutamic acid decarboxylase 65 antibody status, however, HbA_{1c} concentration was apparently lowered more with insulin plus metformin than with insulin plus repaglinide (difference in mean HbA_{1c} −0.27% (−0.55 to 0.00), P=0.052; P=0.037 for the interaction of treatment by glutamic acid decarboxylase 65 status).

The change in HbA_{1c} concentration from baseline seemed to vary according to the number of daily insulin injections at the end of treatment. See bmj.com. The mean self monitored plasma glucose concentration decreased to a similar extent in both treatment groups. At the end of treatment, the concentrations of self monitored plasma glucose appeared lower before and after breakfast in the metformin plus insulin group than in the repaglinide plus insulin group; however, these differences in self monitored plasma glucose did not reach statistical significance (before breakfast −0.54 mmol/l, 95% CI −1.10 to 0.01, P=0.055; 90 minutes after breakfast −0.98 mmol/l, 95% CI −1.96 to 0.00, P=0.051.

There was no significant difference between treatments in the total daily insulin dose at the end of treatment (P=0.233). The proportion of patients who received insulin injections once a day, twice a day, or three times a day at the end of treatment was not significantly different between treatments (P=0.870). Likewise, there were no significant differences between treatment arms in the insulin dose at individual injections during the day.

In both treatment groups, body weight appeared to increase during the first six months but stabilised thereafter. The change in body weight at the end of treatment appeared lower in the metformin plus insulin group than in the repaglinide plus insulin group (P=0.002).

Compliance and study drug exposure

The mean compliance of active study drugs was approximately 96% in both treatment groups. Approximately 30% of patients in each group received a reduced study drug dose, resulting in a mean study drug exposure of 1771 mg/day for metformin and 5.2 mg/day for repaglinide.

Adverse events

The number of either mild or nocturnal hypoglycaemic episodes, as well as the number of episodes of major hypoglycaemia, was not significantly different between treatments. Two serious adverse events potentially related to the study medication were recorded in the repaglinide plus insulin group (suspected allergic reaction to insulin and treatment emergent diarrhoea). See bmj.com.

DISCUSSION

Principal findings

Both treatment groups achieved similar and near optimal glycaemic regulation with similar doses of insulin, which suggests that metformin and repaglinide are equally effective diabetes treatments in such patients. Weight gain, however, seemed less with metformin plus biphasic insulin aspart 70/30 than with repaglinide plus biphasic insulin aspart 70/30.

The rate of hypoglycaemia was not significantly different between interventions. We used near maximal daily doses of metformin (2000 mg) and repaglinide (6 mg) and observed a tendency towards lower pre-breakfast and post-breakfast levels of self monitored plasma glucose with insulin plus metformin. Hence, we cannot exclude the possibility that in our population, higher doses of metformin and repaglinide would have resulted in notable glycaemic differences between treatment groups.

In contrast to present consensus statements recommending that insulin secretagogues are stopped after initiation of insulin therapy,[6] our data suggest a clinically relevant effect of insulin and insulin secretagogues in combination, even in patients with longstanding diabetes in whom beta cell failure otherwise could be anticipated (that is, in the present study patients had preserved beta cell function despite approximately 10 years of diabetes).

Strengths and limitations of study

The initial sample frame of 459 eligible patients is somewhat small; however, we used targeted electronic searches to reach the desired number of participants.

Approached patients who declined to take part were slightly older than those who accepted, but HbA_{1c} concentration and BMI (that is, the main phenotypic characteristics of the population of interest) were not significantly different between these groups. Overall, we do not believe the number of eligible patients or the recruitment process to have confounded the conclusions.

Treatment responses did not seem to be heterogeneous according to baseline patient characteristics such as diabetes duration or previous insulin use, but may have been affected by the presence of autoimmune disease as determined by the presence of glutamic acid decarboxylase 65 antibodies. Although analyses according to patient characteristics were prespecified, these data are only hypothesis generating and should be addressed in future trials. Mean BMI among participants was below 25, concordant with the notion that at least 20% of white patients with type 2 diabetes are not obese.[9-11] Thus, our study population represented white patients with type 2 diabetes having a non-obese phenotype.

Some drug intolerance with respect to gastrointestinal side effects could be anticipated in metformin naive patients. Hence, we used a run-in period to establish study drug tolerance, as well as failure on oral hypoglycaemic agents combination therapy. The run-in period also minimised any confounding effect of chance differences between groups in previous glucose lowering therapies.

We used a treat to target regimen, including patient self titration of insulin dose and increasing the number of injections. Hence, an apparently greater reduction in HbA_{1c} concentration was expected as the number of injections increased. In the present study, self monitored plasma glucose results agreed with HbA_{1c} measurements, and we did not observe differences in insulin doses between treatment groups. The latter supports the notion that observed differences between treatment groups, such as weight gain, resulted from differences between metformin and repaglinide actions (rather than from possible differences in insulin doses)—the key question that we aimed to address.

Body weight was a secondary outcome; thus, our data on this variable must be interpreted cautiously. Nonetheless, BMI, as an adiposity measure, was an inclusion criterion and a stratifying variable. Hence, chance findings were probably less likely to occur for body weight than for other secondary outcomes.

Comparison with other studies

Most studies investigating combination therapy of insulin plus oral hypoglycaemic agents have been of short duration—six months or less,[12-14] and only rarely up to one year.[5 15] Also, most studies failed to reach optimal or near optimal glycaemic regulation.[5 12-15] In the UK Prospective Diabetes Study, patients stopped taking oral hypoglycaemic agents when insulin therapy was initiated.[16] Hence, besides the present study, we are unaware of other such comparative studies in non-obese patients with type 2 diabetes. See bmj.com.

We aimed to lower HbA_{1c} concentration to below 6.5%. This target is associated with a reduced risk of microvascular complications without an adverse increase in the risk of cardiovascular disease or mortality.[17]

Conclusions

In non-obese patients with longstanding type 2 diabetes and glycaemic failure after four months of oral hypoglycaemic agents combination therapy, treatment with metformin plus biphasic insulin aspart 70/30 or repaglinide plus biphasic insulin aspart 70/30 resulted in near optimal and equivalent glycaemic regulation after one year. The difference in the incidence of major hypoglycaemia between the two treatment groups was not significant, although metformin plus biphasic insulin aspart 70/30 seemed to be associated with less weight gain.

Provided that lowering of HbA_{1c} concentration has in itself beneficial vascular effects without adverse effects on mortality, our results of near optimal glycaemic regulation with insulin plus metformin or plus repaglinide suggest these therapies might be used favourably in non-obese patients with type 2 diabetes.

We thank the following companies for their help and support in carrying out this study: Novo Nordisk A/S (Bagsværd, Denmark) and Novo Nordisk Scandinavia A/S (Copenhagen, Denmark) for financial support and study drug supply; The Clinical Development Foundation at Steno Diabetes Center for financial support; Hexal A/S (Hvidovre, Denmark) for study drug supply; and Medisense Danmark (Svedsted, Denmark) for technical supply. We thank the following individuals from Novo Nordisk A/S for their statistical assistance: Helle Frimer-Larsen; Helle Lynggaard; Patrick Dykiel; and Ralph Eriksen. We thank Mari-Anne Gall; Kirstine Brown Frandsen; Benedikte Østergaard; Mette Harring, Christina Fischer, Tina Kuni, Julius Vaz, Harry Itamery, Danilo Verge, Brian Hilberdink, Niels Christiansen, Anders Dyhr-Toft, Titus Gylvin; Plamen Kozlowski; Zsolt Bosnyak; and Anders Dejgaard for their enthusiastic support in initiating and carrying out the trial. We thank the following laboratory technicians at Steno Diabetes Center: Ulla Meng Smidt; Tina Ragnholm Juhl; Berit Ruud Jensen; Lotte Pietraszek; and Ingelise Rossing. We also thank Brian Molsing for his technical support and Ingelise Holstein for allocating the randomised treatments. Finally, we thank Jukka Rantanen from the Department of Pharmaceutics and Analytical Chemistry at the Danish University of Pharmaceutical Sciences (Copenhagen, Denmark) for his pharmaceutical analyses.

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Funding: Novo Nordisk A/S, Novo Nordisk Scandinavia A/S, and the Clinical Development Foundation at Steno Diabetes Center co-sponsored the study financially. Novo Nordisk A/S and Novo Nordisk Scandinavia A/S supplied biphasic insulin aspart 70/30, repaglinide, and repaglinide placebo tablets. Hexal A/S supplied metformin and metformin placebo tablets. Medisense Danmark supplied blood glucose hand measurement devices and test strips. Steno Diabetes Center housed the database and Novo Nordisk A/S performed the statistical analyses. Otherwise, the sponsors had no role in design and conduct of the study; collection, management, and interpretation of the data; or preparation, review, and approval of the manuscript.

Competing interests: SSL, LT, MF, BBN, BVH, OP, H-HP, and AAV have reported equity in Novo Nordisk A/S. LT, H-HP, and AAV have received funds from Novo Nordisk A/S for research. SSL and AAV have received fees from Novo Nordisk A/S for speaking and AAV has received fees from Novo Nordisk A/S for organising education. SSL, LT, MF, BBN, BVH, OP, H-HP, and AAV are present or former employees at Steno Diabetes Center, Gentofte, Denmark. Steno Diabetes Center is an independent academic institution owned by Novo Nordisk A/S and the Novo Nordisk Foundation.

Data sharing: Full study protocol, statistical analysis plan, and statistical code available from the corresponding author.

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Accepted: 5 August 2009

Differences in atherosclerosis according to area level socioeconomic deprivation: cross sectional, population based study

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Cite this as: *BMJ* 2009;339:b4170
doi: 10.1136/bmj.b4170

ABSTRACT

Objectives To examine the relation between area level social deprivation and ultrasound markers of atherosclerosis (common carotid intima-media thickness and plaque score), and to determine whether any differences can be explained by "classic" (currently recognised) or "emerging" (novel) cardiovascular risk factors.

Design Cross sectional, population based study.
Setting NHS Greater Glasgow Health Board area.
Participants 666 participants were selected on the basis of how their area ranked in the Scottish Index of Multiple Deprivation 2004. Approximately equal numbers of participants from the most deprived areas and the least deprived areas were included, as well as equal numbers of men and women and equal numbers of participants from each age group studied (35-44, 45-54, and 55-64 years).
Main outcome measures Carotid intima-media thickness and plaque score, as detected by ultrasound.
Results The mean age and sex adjusted intima-media thickness was significantly higher in participants from the most deprived areas than in those from the least deprived areas (0.70 mm (standard deviation 0.16 mm) *v* 0.68 mm (0.12 mm); P=0.015). On subgroup analysis, however, this difference was only apparent in the highest age tertile in men (56.3-66.5 years). The difference in unadjusted mean plaque score between participants from the most deprived and those from the least deprived areas was more striking than the difference in intima-media thickness (least deprived 1.0 (standard deviation 1.5) *v* most deprived 1.7 (standard deviation 2.0); P<0.0001). In addition, a significant difference in plaque score was apparent in the two highest age tertiles in men (46.8-56.2 years and 56.3-66.5 years; P=0.0073 and P<0.001) and the highest age tertile in women (56.3-66.5 years; P<0.001).

WHAT IS ALREADY KNOWN ON THIS TOPIC

Coronary heart disease is more prevalent in areas of relative social deprivation than in socioeconomically advantaged areas
This health gap is not satisfactorily explained by currently recognised ("classic") cardiovascular risk factors
A number of novel ("emerging") risk factors have been identified that might contribute to deprivation based differences in cardiovascular disease

WHAT THIS STUDY ADDS

Indices of atherosclerosis (carotid intima-media thickness and plaque presence), as determined by ultrasound, are significantly higher in people from more deprived areas; plaque score being the more sensitive marker
Adjustment for classic cardiovascular risk factors and emerging risk factors associated with insulin resistance, inflammation, endothelial dysfunction, and haemostasis does not abolish the deprivation based difference in ultrasound markers of atherosclerosis
Adjustment for individual level markers of socioeconomic status as well as classic and emerging risk markers likewise does not abolish the difference in carotid intima-media thickness between men from the least deprived areas and those from the most deprived areas

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This article is an abridged version of a paper that was published on bmj.com. Cite this article as: *BMJ* 2009;339:b4170

The difference in intima-media thickness between most deprived and least deprived males remained significant after adjustment for classic risk factors, emerging risk factors, and individual level markers of socioeconomic status (P=0.010). Adjustment for classic risk factors and emerging cardiovascular risk factors, either alone or in combination, did not abolish the deprivation based difference in plaque presence (as a binary measure; adjusted odds ratio of 1.73, 95% confidence interval 1.07 to 2.82). However, adjustment for classic risk factors and individual level markers of early life socioeconomic status abolished the difference in plaque presence between the most deprived and the least deprived individuals (adjusted odds ratio 0.94, 95% CI 0.54 to 1.65; P=0.84).
Conclusions Deprivation is associated with increased carotid plaque score and intima-media thickness. The association of deprivation with atherosclerosis is multifactorial and not adequately explained by classic or emerging risk factors.

INTRODUCTION

The higher incidence of coronary heart disease in areas of socioeconomic deprivation compared with socioeconomically advantaged areas is well documented.[1-3] Although "classic" (currently recognised) risk factors go some way towards explaining this gradient,[4] they do not explain all the difference.[5-7] In recent years, novel biomarkers associated with insulin resistance, inflammation, and endothelial dysfunction have emerged as potential cardiovascular risk factors.[8] Whether any of these markers helps explain the socioeconomic gradient in coronary heart disease remains to be seen.

Several studies have examined the relation between socioeconomic status and ultrasound markers of atherosclerosis. Most studies have examined individual level measures of socioeconomic position (for example, income, education, occupation, housing tenure) and their relation to carotid intima-media thickness.[9-15] However, a study in Pittsburgh found associations between community level socioeconomic status and both carotid intima-media thickness and carotid plaque occurrence.[16]

We measured a range of "classic" and "emerging" cardiovascular risk factors, with a view to examining variables that could potentially explain the difference in prevalence of cardiovascular disease between most and least deprived populations.

METHODS

Study population

Practices in the Greater Glasgow Health Board area were selected on the basis of the Scottish Index of Multiple Deprivation 2004,[17] which ranks small areas on the basis of multiple deprivation indicators across six domains. Five general practices in areas in the bottom 5% of all areas classed by the Scottish Index of Multiple Deprivation (that is, the most deprived areas) and five practices in areas in the top 20% (that is, the least deprived areas) were approached. All practices agreed to participate.

From these practices, 12 groups of 300 participants were selected according to strata defined by the combination of Scottish Index of Multiple Deprivation classification, gender, and age group (35-44, 45-54, and 55-64 years).

Study protocol

Participant visits were conducted between December 2005 and May 2007. Participants completed questionnaires and underwent measurement of height; weight; blood pressure; heart rate; hip, waist, and mid-thigh circumference; and lung function. Following a fast, participants provided blood samples for biochemical analyses, and carotid ultrasound was performed.

All ultrasound scans were analysed by the same reader, who was blinded to the identities of the participants. Reader reproducibility was assessed by repeat reading of a proportion of the scans.

Outcome measures

The primary outcome was mean common carotid intima-media thickness. The secondary outcome was plaque score,[18] which was determined by counting the number of plaques and adjusting for unreadable images.

Biochemical analysis of risk factors

The classic risk factors of cholesterol (total cholesterol, low density lipoprotein, and high density lipoprotein), triglyceride, and glucose concentrations were measured. The following emerging risk factors were assessed: insulin, adiponectin, leptin, high sensitivity C reactive protein, interleukin 6, intercellular adhesion molecule 1, von Willebrand factor, fibrinogen, D-dimer, and tissue plasminogen activator antigen. Questions on habitual physical activity at work and in recreation were included in the questionnaire.

Statistical analysis

We compared population characteristics between deprivation groups. For intima-media thickness, an analysis was performed of thickness versus age for men and women in each deprivation category. For analysis of plaque score, negative binomial regression was carried out. For multivariate models involving plaque, plaque presence was used as the dependent variable and logistic regression was used for modelling.

RESULTS

Overall, 2712 invitations to participate were issued and 666 individuals completed study visits, giving an overall response rate of 24.6%. The least deprived group comprised 175 men and 167 women, and the most deprived group consisted of 159 men and 165 women.

Total cholesterol was lower in the most deprived group than in the least deprived group (4.95 mmol/l *v* 5.29 mmol/l; P<0.0001). High density lipoprotein cholesterol was lower in the most deprived group (1.30 mmol/l *v* 1.43 mmol/l; P<0.0001) as was low density lipoprotein (2.86 mmol/l *v* 3.16 mmol/l; P<0.0001),

Differences in ultrasound markers of atherosclerosis between participants from the most deprived areas and those from the least deprived areas

	Least deprived(n=342)	Most deprived(n=324)	Least minus most deprived (adjusted for age and sex(95% CI))	P
Mean (SD) carotid intima-media thickness (mm)	0.68 (0.12)	0.70 (0.16)	−0.02 (−0.04 to −0.00)	0.015
Data missing	23	29		
Mean (SD) plaque score	1.0 (1.5)	1.7 (2.0)		<0.0001*
Number of plaques (%)				
0 plaques	193 (56.9%)	130 (41.7%)		<0.0001 for trend*
1-2 plaques	101 (29.8%)	89 (28.5%)		
>2 plaques	45 (13.3%)	93 (29.8%)		
Data missing	3	12		

*Not adjusted for age and sex.

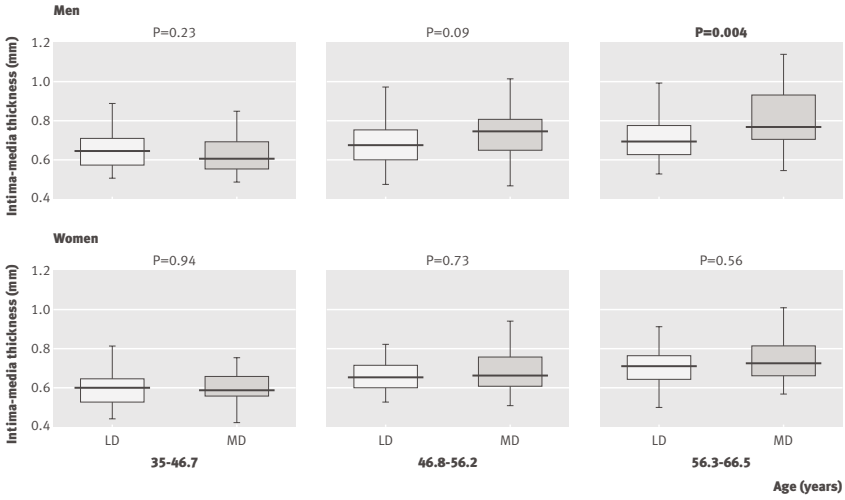

Fig 1 | Intima-media thickness by age tertile and deprivation category. LD=least deprived, MD=most deprived

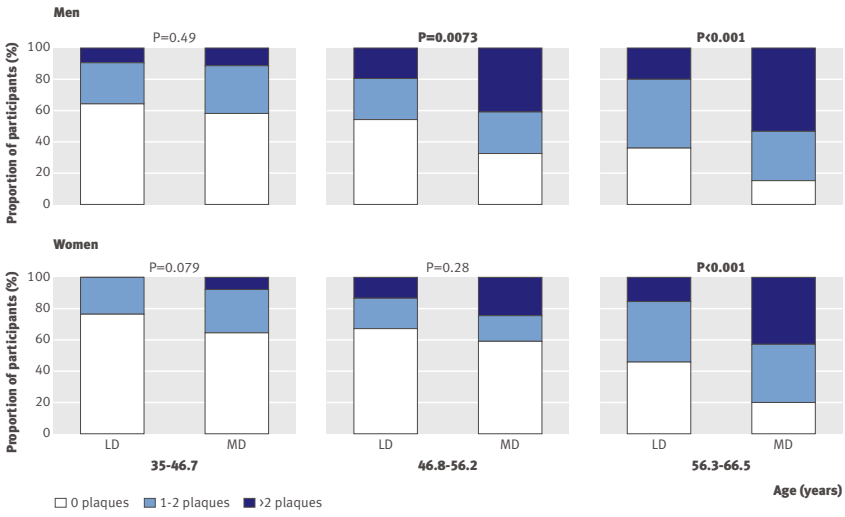

Fig 2 | Plaque score by age tertile and deprivation category. LD=least deprived, MD=most deprived

so the low density lipoprotein/high density lipoprotein ratio did not differ between the two groups.

Blood pressure did not differ between the two groups. The proportion of current smokers in the most deprived group was significantly higher than that in the least deprived group (40.4% *v* 6.1%).

Indices of insulin resistance, dysglycaemia, and obesity were significantly higher in the most deprived group (P<0.05 for all). The difference in adiponectin concentration between the two groups was not significant.

Markers of chronic inflammation and endothelial dysfunction were significantly different between the two groups (all P<0.0001). Fibrinogen and D-dimer concentrations were higher in the most deprived category (P<0.0001 and P=0.0018, respectively), but no difference was observed in tissue plasminogen activator antigen concentration (P=0.18).

Carotid ultrasound analysis

Differences in ultrasound markers of atherosclerosis are shown in the table. The age and sex adjusted difference in mean carotid intima-media thickness between the most deprived group and the least deprived group was 0.02 mm (P=0.015). The difference in mean carotid intima-media thickness between participants in most and least deprived areas was statistically significant for men (P=0.044) but not for women (P=0.77).

Figures 1 and 2 show the differences in carotid intima-media thickness and plaque score for each gender, separately split by age tertile. The expected increase in carotid intima-media thickness with age is present; however, the difference in carotid intima-media thickness between the most deprived group and the least deprived group only reached statistical significance in the highest age tertile (56.3-66.5 years) in men and did not achieve statistical significance in women at any age. By contrast, the difference in plaque score between the most deprived group and the least deprived group was highly significant in men in the two highest age tertiles (46.8-56.2 years and 56.3-66.5 years; both P<0.01) and in women in the highest age tertile (56.3-66.5 years; P<0.001).

Multivariate analyses for carotid intima-media thickness

The following variables were significant correlates for age adjusted carotid intima-media thickness in men: triglycerides (positive association; P=0.0092); high density lipoprotein cholesterol (negative association; P=0.044); and systolic blood pressure (positive association; P=0.028).

Adjusting for the classic risk factors of triglycerides, low density lipoprotein cholesterol, high density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, and history of hypertension failed to attenuate the difference in carotid intima-media thickness between most deprived men and least deprived men (P=0.031).

In further models, "emerging" risk factors representing insulin resistance, inflammatory factors, and haemostasis were adjusted for. With all classic and emerging risk factors added, and physical activity and individual level markers of socioeconomic status included, the difference in carotid intima-media thickness between most deprived and least deprived males remained significant (P=0.010).

Multivariate analyses for plaque score

On age and sex adjusted analyses, the following risk factors were significant predictors of plaque presence: log triglycerides (P=0.0016); systolic blood pressure (P=0.0079); diastolic blood pressure (P=0.049); current smoking (P<0.0001); log intercellular adhesion molecule 1 (P=0.00028); and fibrinogen (P=0.023). Height (P=0.00013) and hip circumference (P=0.00014) were inversely associated with plaque score.

In a model that adjusted for all classic and novel risk factors plus physical activity, the difference in plaque presence between the most deprived and the least deprived individuals remained significant (adjusted odds ratio 1.73, 95% confidence interval 1.07 to 2.82; P=0.026). In general terms, individuals from the most deprived areas had around a 1.5-fold to 2-fold higher risk of plaque presence than those from least deprived areas.

Inclusion of individual level markers of early life socioeconomic status and classic risk factors abolished the difference in plaque presence between individuals from the most deprived areas and those from the least deprived areas (adjusted odds ratio for plaque presence 0.94, 95% CI 0.54 to 1.65; P=0.84).

DISCUSSION

Carotid plaque score and intima-media thickness were significantly worse in participants from the bottom 5% of all areas classed by the Scottish Index of Multiple Deprivation than in individuals living in areas classified as being in the top 20%. Although there were clear differences in biomarkers of chronic inflammation between participants from the two groups, neither these factors nor classic risk factors satisfactorily explained the increased atherosclerosis burden in the lower socioeconomic status group.

A difference between the two groups in plaque score appeared at an earlier age than a difference in intima-media thickness. The difference in intima-media thickness between participants from the least and most deprived areas did not reach statistical significance in women at any age tertile studied. This finding is not surprising given that the difference in men only reached statistical significance in the highest age tertile and the fact that atherosclerosis tends to develop around a decade later in women than in men.

Adjustment for classic risk factors did not fully explain the difference in ultrasound markers of atherosclerosis between participants from most and least deprived areas.

Inflammatory pathways are involved in atherosclerosis,[19] and significant differences in inflammatory markers were noted between deprivation categories. However, none of the measured markers of inflammation, insulin resistance, or haemostasis had a significant impact on the difference in plaque presence between the two deprivation groups, with area level deprivation remaining a significant predictor even once all classic and emerging risk factors were included in the model. These findings are broadly consistent with those from the women's health study, in which classic and emerging risk factors only partly explained the inverse relationship between educational attainment and cardiovascular risk.[20]

Only by adjusting for individual level markers of socioeconomic status was the difference in plaque presence between participants from the least and most deprived areas abolished. Given that area level and individual level markers of socioeconomic status are likely to be highly correlated, this outcome might be the result of overadjustment.

Strengths and limitations of this study

The setting of Glasgow, Scotland, was excellent for this study because a wide range of deprivation and life expectancy can be found within the city. The very complete dataset, with relatively few missing results, is also a strength of this study.

Limitations of this study include the fact that only individuals from the two extremes of area level social deprivation were included. Another concern is the question of whether study participants differed from non-participants. It is possible that the "worried well" and the "healthy deprived" would preferentially volunteer for this study, thus minimising potential differences between least and most deprived communities. We compared study participants with individuals in the anonymised data obtained from the General Practice Administration System for Scotland, which demonstrated differences between participants and non-participants and showed that those who participated had a higher level of recognised morbidity than those who did not participate.

A further concern is whether the findings from this study are generalisable to populations other than those living in the NHS Greater Glasgow area. However, ongoing research suggests that the deprivation profile of Glasgow is not unique in the United Kingdom.

Conclusions and policy implications

This study demonstrates the significance of area level socioeconomic deprivation as a predictor of atherosclerosis. Health status is a reflection not only of features of the individual but also of wider social and economic influences, health and social services, early life experiences, and environmental factors. The analyses reported here focused on biological pathways that might explain the disparity (for example, insulin resistance, inflammation, and haemostasis). Further analyses focusing on the relative strengths of different pathways may help in unravelling the multifactorial nature of health inequalities.

Acknowledgments: See bmj.com.

Contributors: See bmj.com.

Funding: This study was funded by the Glasgow Centre for Population Health, a partnership between NHS Greater Glasgow and Clyde, Glasgow City Council, and the University of Glasgow that is supported by the Scottish government. All study data were held by the Robertson Centre for Biostatistics and remained blinded until after the end of data collection. Study data were then unblinded and analysed by the Robertson Centre for Biostatistics. Furthermore, the Glasgow Centre for Population Health had no competing interest (financial or otherwise) related to the findings of the study.

Competing interests: None declared.

Ethical approval: The study was reviewed and approved by the Glasgow Royal Infirmary Research Ethics Committee; all participants gave written informed consent.

Data sharing: No additional data available.

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Accepted: 2 June 2009

A memorable night

Some years ago, I was the doctor on call for primary and prehospital emergency care. An evening call came in: "Boat carrying refugees has run aground in local waters. Many stranded at cliff bottom."

I declined to be winched down to the boat, knowing that the rescued passengers would need to come up sooner or later. They were ferried to a makeshift reception centre, and I made my way there, wondering what to expect. I was not prepared for the scene—dozens of men, women, and children of many different nationalities, all sprawled exhausted across any available seat and the floor. Their initial relief at having survived was soon replaced by complaints of thirst, pains, and emotional distress.

Cultural and language differences were a hindrance, but my stethoscope identified me as a source of help. No one spoke a mutual language sufficiently for effective doctor-patient communication, and my request for an interpreter resulted in a sheet of paper listing identical medical questions in two different languages, but unfortunately no answers. History taking proved impossible, but we did what we could.

I examined an infant on the baby changing facilities of the tiny women's toilet; the mother claimed that she was born on the boat. This could never be proved, but her clamped umbilical cord was still attached. I wondered how desperate the woman must have been to board that boat.

Social needs for water, food, and shelter took precedence over ill health, though my intervention was needed to obtain them. Soon food, clothes, nappies, and baby milk appeared as the local community pulled together.

Six weeks later, I gave birth to my first child in the comfort and security of a hospital, and, as I cradled him in my arms, I once again contemplated those refugees. What fear, desperation, or hope for a better life had led them to put to sea and trust their lives to a money grabbing captain? Old and overladen, the boat had not carried them to distant promised lands and welcoming relatives, instead their voyage had ended abruptly on the rocky coast outside my hospital window. For many, perhaps this was enough, as they successfully sought asylum in various European countries; for others, the outcome was more protracted.

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Patient consent: not required (patient anonymised, dead, or hypothetical).

Cite this as: *BMJ* 2009;339:b4359

pico

Evaluation of modernisation of adult critical care services in England: time series and cost effectiveness analysis

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Cite this as: *BMJ* 2009;339:b4353
doi: 10.1136/bmj.b4353

This is a summary of a paper that was published on bmj.com as *BMJ* 2009;339:b4353

STUDY QUESTION What was the impact and cost effectiveness of a programme to transform adult critical care throughout England that was initiated in late 2000?

SUMMARY ANSWER In the six years after 2000 there were reductions in critical care transfers, unplanned discharges at night, readmission rates, and hospital mortality, which fell by 13.4%. The mean annual net monetary benefit increased significantly after 2000, indicating that the changes were highly cost effective.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS There have been conflicting claims as to the impact of increases in funding for adult critical care in the NHS in England since 2000 and specific interventions to "modernise" services. There have been major improvements in processes and outcomes of care, and collectively the interventions associated with the modernisation of critical care represent a highly cost effective use of NHS resources.

Participants and setting

349 817 admissions to 96 critical care units in England during the period 1998-2006 from the case mix programme database of the Intensive Care National Audit and Research Centre.

Design, size, and duration

The critical care programme got underway at the end of 2000. We compared trends in inputs (beds, costs), processes (transfers between units, discharge practices, length of stay, readmissions), and outcomes (unit and hospital mortality) for 1998-2000 with data for 2000-6 after adjusting for case mix. Differences in annual costs and quality adjusted life years (QALYs) were used to calculate incremental net monetary benefits (valuing a QALY gain at £20 000). We adopted a hospital perspective that included all costs for hospital admissions during an episode.

Results

Annual expenditure on critical care increased in real terms from £700m (1999-2000) to £1bn (2005-6). This was associated with a 35% increase in the number of staffed beds in general intensive care units. After 2000 the declines in the proportion of transfers out of units to another unit, unplanned discharges at night, and readmissions within 48 hours were faster than during 1998-2000. Unit and hospital mortality did not change between 1998 and 2000 but subsequently fell by an average of 2.0% and 2.4% a year, respectively. Mean length of stay increased before 2000 by 0.243 days a year but by only 0.036 days a year afterwards (P<0.001). After 2000 a decline in incremental costs and an increase in mean lifetime QALYs resulted in a positive incremental net monetary benefit of £692 (P=0.008).

Results of sensitivity analysis

Sensitivity analysis had little effect on the main findings. The impact of using national estimates of unit costs, including a larger high dependency component to costs, using summary case mix adjustment, using general population estimates for lifetime QALY gains, and valuing a QALY at £30 000 produced similar or larger estimates of net monetary benefit.

Bias, confounding, and other reasons for caution

Other concurrent changes might have contributed to the improvements observed. While the final quarter of 2000 represented the optimum time point to mark the start of the interventions, adoption did not occur until later in many units.

Study funding/potential competing interests

The study was funded by the NIHR SDO research and development programme (grant SDO/133/2006). AH was supported by a MRC special training fellowship in health services research.

ADJUSTED RELATIVE RISK FOR ANNUAL CHANGE IN DISCHARGES, READMISSIONS, AND MORTALITY

	RR (95% CI) 1998-2000	RR (95% CI) 2000-6	P value*
Transfers out of units	1.03 (0.99 to 1.07)	0.89 (0.87 to 0.90)	<0.001
Early discharges	0.92 (0.89 to 0.94)	0.89 (0.88 to 0.90)	0.101
Unplanned discharges at night (midnight to 4 59 am)	1.03 (0.97 to 1.09)	0.92 (0.90 to 0.94)	0.008
Readmissions within 48 hours	1.03 (0.98 to 1.07)	0.95 (0.94 to 0.97)	0.006
Unit mortality	1.00 (0.99 to 1.01)	0.98 (0.98 to 0.98)	<0.001
Hospital mortality	1.00 (0.99 to 1.01)	0.98 (0.98 to 0.98)	<0.001

* For difference in trends

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pico

Food incentives to improve completion of tuberculosis treatment: randomised controlled trial in Dili, Timor-Leste

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EDITORIAL by Maher

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Cite this as: *BMJ* 2009;339:b4248
doi: 10.1136/bmj.b4248

This is a summary of a paper that was published on bmj.com as *BMJ* 2009;339:b4248

STUDY QUESTION Among adults with newly diagnosed pulmonary tuberculosis in Timor-Leste, does the provision of whole food (compared with nutritional advice about a balanced diet) improve completion of eight months' treatment for tuberculosis?

SUMMARY ANSWER Overall, 76-78% of patients completed eight months of treatment. Food did not improve treatment completion rates.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Adherence to treatment is central to tuberculosis control. Food incentives are attractive because of the well described link between malnutrition and tuberculosis. There is unconvincing evidence of direct benefit on a range of clinical outcomes. In Timor-Leste, food incentives led to modestly higher weight gain in patients with tuberculosis but did not improve treatment adherence or successful completion of treatment.

Design

Parallel group randomised (allocation concealed) controlled trial. Outcomes were assessed remotely, blinded to allocation status. Participants started standard tuberculosis treatment and were randomly assigned to intervention (nutritious, culturally appropriate daily meal (weeks 1-8) and food package (weeks 9-32), n=137) or control groups (nutritional advice, n=133). Randomisation sequence was computer generated with allocation concealment by sequentially numbered, opaque, sealed envelopes.

Participants and setting

270 adults aged ≥18 with previously untreated newly diagnosed pulmonary tuberculosis at three primary care clinics in Dili, Timor-Leste.

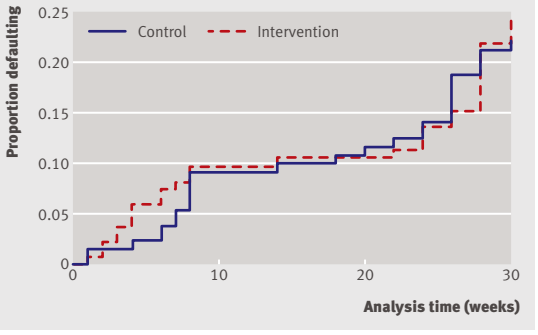
Primary outcome(s)

The primary outcome measure was completion of treatment (including cure) at the end of treatment (32 weeks). Secondary outcomes included treatment adherence, weight gain, and sputum smear clearance.

Main results and the role of chance

Most patients with tuberculosis were poor, malnourished men living close to the clinics; 265 of 270 patients enrolled (98%) contributed to the analysis. The intervention had no significant beneficial or harmful impact on the outcome of treatment (76% *v* 78% completion, 95% confidence interval of difference −11% to 9%; P=0.7) or adherence (93% for both groups, −1.7% to 1.7; P=0.7) but did lead to improved weight gain at the end of treatment (10.1% *v* 7.5% improvement, 0.1% to 5.1%; P=0.04). In a subgroup analysis of patients with positive results on sputum smears at diagnosis there were clinically important improvements in one month sputum clearance (85% *v* 67%, −4% to 34%; P=0.13) and completion of treatment (78% *v* 68%, −9% to 27%; P=0.3).

TIME TO TREATMENT DEFAULT BY GROUP



Harms

Itch was more common in the intervention group (21% *v* 9%, 3% to 18%; P<0.01).

Bias, confounding, and other reasons for caution

The strict selection of participants to this randomised controlled trial might have excluded patients most likely to benefit. For ethical reasons, we were required to differentiate between patients in the control and intervention groups by spacing their attendance at the clinic. This might have been an unanticipated barrier to effective treatment, counteracting any positive effect of food provision. Civil conflict in Dili in the later part of the study affected adherence to treatment in a substantial number of patients (completion rates 84% *v* 53%, P<0.001).

Generalisability to other populations

In this setting, food supplementation did not significantly improve treatment completion, treatment adherence, or treatment outcome. There was a modest increase in weight. Further studies with a larger sample size (and a wider selection of patients from different settings) will be required to confirm or refute these findings.

Study funding/potential competing interests

The study was funded by the Unicef/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, which also provided a PhD scholarship for NM. Australia's National Health and Medical Research Council provides salary support for PMK. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Trial registration number

Clinical Trials NCT0019256.

pico

Outcomes and costs of primary care surveillance and intervention for overweight or obese children: the LEAP 2 randomised controlled trial

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Cite this as: *BMJ* 2009;339:b3308
doi: 10.1136/bmj.b3308

This is a summary of a paper that was published on bmj.com as *BMJ* 2009;339:b3308

STUDY QUESTION Does primary care screening for overweight and mildly obese children followed by brief structured counselling improve body mass index?

SUMMARY ANSWER No, the intervention did not improve body mass index, physical activity, or nutrition at 12 months.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS National policies in many countries promote primary care surveillance and brief counselling to reduce childhood obesity, but two systematic reviews found no evidence to corroborate this. Our trial showed this approach to be ineffective, and it would be very costly if implemented universally for all affected children.

Design
This randomised controlled trial was nested within a baseline cross sectional survey of body mass index (BMI). Using computer-generated random numbers, an independent biostatistician randomised each child stratified by general practitioner and by overweight versus obese status. Randomisation and outcomes measurement were blinded.

The GPs attended two 2½ hour group training sessions for training in brief, solution focused, family therapy. Each GP then conducted two simulated patient sessions during working hours. The research team invited intervention families to attend their GP for four standard consultations over 12 weeks targeting change in nutrition, physical activity, and sedentary behaviour, supported by purpose-designed written materials.

Participants and setting
Sixty six GPs participated from 45 family practices in Melbourne, Australia, and 3958 children aged 5 years 0 months to 9 years 11 months visited these GPs in May 2005-July 2006 and took part in the BMI survey. Children were eligible for the trial if overweight or obese by International Obesity Taskforce criteria; very obese children (UK BMI z score ≥3.0) were excluded as inappropriate for the intervention. Of 781 eligible children, 258 (33%) entered the trial and were randomised to intervention (n=139) or control (n=119) groups.

Primary outcome(s)
The primary measure was BMI at six and 12 months after randomisation. Secondary measures were waist circumference, physical activity, nutrition score, and child health related quality of life.

Main results and the role of chance
Attrition was 3.1% at six months and 6.2% at 12 months. Differences were adjusted for socioeconomic status, age, sex, and baseline BMI. Adjusted mean differences (intervention−control) at six and 12 months were, for BMI, −0.12 (95% CI −0.40 to 0.15, P=0.4) and −0.11 (−0.45 to 0.22, P=0.5); for waist girth, 0.12 (−0.98 to 1.22, P=0.8) and 0.12 (−1.12 to 1.37, P=0.8); for physical activity, 24 (−4 to 52, P=0.09) and 11 (−26 to 49, P=0.6); and, for nutrition score, 0.2 (−0.03 to 0.4, P=0.1) and 0.1 (−0.1 to 0.4, P=0.2) (see table).

Harms
There was no evidence of harm to children's health related quality of life, body dissatisfaction, or self esteem. Health sector costs were $A1317 per child for the intervention and $A81 per control child, a difference of $A1236 (95% CI $A1205 to $A1267).

Bias, confounding, and other reasons for caution
The general practitioners were self selected, only a third of families with an eligible child took up the intervention, and families were not blind to study group membership. However, these limitations would promote, not reduce, differences between the groups, so they don't explain our negative findings.

Generalisability to other populations
Our results are likely to be applicable to many Western populations.

Study funding/potential competing interests
This trial was funded by Australian National Health and Medical Research Council. There were no competing interests.

Trial registration number
ISRCTN 52511065.

EFFECTS AT 12 MONTHS OF PRIMARY CARE SURVEILLANCE AND INTERVENTION FOR OVERWEIGHT OR OBESE CHILDREN

	Mean (SD) measure		Adjusted difference	
Outcome	Intervention	Control	Mean (95% CI)	P value
Body mass index	20.8 (2.8)	21.0 (2.4)	-0.11 (-0.45 to 0.22)	0.5
Waist circumference	72.2 (9.1)	72.2 (8.4)	0.12 (-1.12 to 1.37)	0.8
Physical activity	344 (136)	332 (131)	11 (-26 to 49)	0.6
Nutrition score	3.9 (1.0)	3.7 (1.1)	0.1 (-0.1 to 0.4)	0.2
Quality of life	80.2 (12.1)	79.4 (12.7)	1.6 (-1.5 to 4.7)	0.3
Body dissatisfaction	0.9 (1.1)	0.9 (1.0)	-0.07 (-0.33 to 0.19)	0.6