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Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis

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STUDY QUESTION

What are the comparative effectiveness, safety, and cost effectiveness of long acting insulin and intermediate acting insulin for patients with type 1 diabetes?

SUMMARY ANSWER

Long acting insulin analogs are probably superior to intermediate acting insulin analogs, although the difference is small for hemoglobin A_{1c} and they are more costly.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Newer long acting insulin analogs might be more effective and safer than intermediate acting insulin in patients with type 1 diabetes but are more expensive. In patients with type 1 diabetes, long acting insulin is statistically significantly superior to intermediate acting insulin for glycemic control and harms (weight gain and severe hypoglycemia), but glargine and detemir are more costly than neutral protamine Hagedorn (NPH) in most cases.

Selection criteria for studies

We searched Medline, the Cochrane Central Register of Controlled Trials, Embase, and grey literature from the earliest date through January 2013. We included randomized controlled trials (RCTs) or non-randomized studies of long acting (glargine, detemir) and intermediate acting (NPH, lente) insulin for adults with type 1 diabetes.

Primary outcome(s)

The primary outcome was glycated hemoglobin (A_{1c}).

Main results and role of chance

In network meta-analysis (26 RCTs), glargine once daily (mean difference -0.39%, 95% confidence interval -0.59% to -0.19%), detemir once daily (-0.26%, -0.48% to -0.03%), and detemir once/twice daily (-0.36%, -0.65% to -0.08%) significantly reduced hemoglobin A_{1c} compared with NPH once daily. Differences in network meta-analysis were observed between long acting and intermediate acting insulin for severe hypoglycemia (16 RCTs; detemir once/twice daily versus NPH once/twice daily: odds ratio 0.65, 0.50 to 0.85) and weight gain (13 RCTs; detemir once daily versus NPH once/twice daily: mean difference 4.04 kg, 3.06 to 5.02 kg; detemir once/twice daily versus NPH once daily: -5.51 kg, -6.56 to -4.46 kg; glargine once daily versus NPH once daily: -5.14 kg, -6.07 to -4.21 kg). Compared with NPH, detemir was less costly and more effective in 3/14 cost effectiveness analyses and glargine was less costly and more effective in 2/8 cost effectiveness analyses. The rest of the cost effectiveness

Results for network meta-analysis of randomized clinical trials: haemoglobin A_{1c} in % (26 trials including 6776 patients)

Treatment comparison	Mean difference (95% CI)
NPH (qid) v NPH (od/bid)	0.32 (-0.15 to 0.79)
NPH (od) v NPH (od/bid)	0.31 (0.02 to 0.60)
Detemir (od/bid) v NPH (od/bid)	-0.05 (-0.28 to 0.18)
Detemir (qid) v NPH(od/bid)	-0.07 (-0.54 to 0.39)
Detemir (od) v NPH (od/bid)	0.05 (-0.25 to 0.36)
Glargine (bid) v NPH (od/bid)	-0.08 (-0.54 to 0.39)
Glargine (od) v NPH (od/bid)	-0.08 (-0.32 to 0.16)
NPH (od) v NPH (qid)	-0.01 (-0.46 to 0.44)
Detemir (od/bid) v NPH (qid)	-0.37 (-0.84 to 0.10)
Detemir (qid) v NPH (qid)	-0.40 (-0.96 to 0.17)
Detemir (od) v NPH (qid)	-0.27 (-0.73 to 0.20)
Glargine (bid) v NPH (qid)	-0.40 (-0.97 to 0.17)
Glargine (od) v NPH (qid)	-0.40 (-0.80 to 0.00)
Detemir (od/bid) v NPH (od)	-0.36 (-0.65 to -0.08)
Detemir (qid) v NPH (od)	-0.39 (-0.83 to 0.06)
Detemir (od) v NPH (od)	-0.26 (-0.48 to -0.03)
Glargine (bid) v NPH (od)	-0.39 (-0.84 to 0.06)
Glargine (od) v NPH (od)	-0.39 (-0.59 to -0.19)
Detemir (qid) v detemir (od/bid)	-0.02 (-0.49 to 0.45)
Detemir (od) v detemir (od/bid)	0.11 (-0.17 to 0.38)
Glargine (bid) v detemir (od/bid)	-0.03 (-0.50 to 0.45)
Glargine (od) v detemir (od/bid)	-0.03 (-0.27 to 0.22)
Detemir (od) v detemir (qid)	0.13 (-0.34 to 0.59)
Glargine (bid) v detemir (qid)	0.00 (-0.57 to 0.57)
Glargine (od) v detemir (qid)	-0.01 (-0.41 to 0.40)
Glargine (bid) v detemir (od)	-0.13 (-0.60 to 0.34)
Glargine (od) v detemir (od)	-0.13 (-0.37 to 0.10)
Glargine (od) v glargine (bid)	0.00 (-0.41 to 0.40)

bid=twice daily; NPH=neutral protamine Hagedorn; od=once daily; qid=four times daily.

analyses found that detemir and glargine were more costly but more effective than NPH. Glargine was not cost effective compared with detemir in 2/2 cost effectiveness analyses.

Bias, confounding, and other reasons for caution

We excluded an RCT written in Japanese and some of our results were based on one included study (for example, retinopathy, quality of life). We focused on cost effectiveness results that were dominant. However, many of the included cost effectiveness analyses found that detemir was more costly and more effective than NPH and that glargine was more costly and more effective than NPH.

Study funding/potential competing interests

This systematic review was funded by the Canadian Institutes for Health Research/Drug Safety and Effectiveness Network (CIHR/DSEN).

Adherence to healthy lifestyle and risk of gestational diabetes mellitus: prospective cohort study

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STUDY QUESTION

Is a healthy lifestyle profile before pregnancy associated with a reduced risk of gestational diabetes?

SUMMARY ANSWER

Compared with women who did not meet any of the low risk factors assessed (healthy body weight, healthy diet, regular exercise, and not smoking), those who met all four criteria had an 83% lower risk of gestational diabetes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Although several potentially modifiable factors of gestational diabetes have been identified, the joint effect of them is unknown. This study suggests that adherence to a healthy lifestyle profile before pregnancy is associated with a substantially lower risk, which applies to both normal weight and overweight/obese women.

Participants and setting

The study population comprised female nurses who had a singleton live birth during 1989 to 2001 in the Nurses' Health Study II in the United States.

Design, size, and duration

We conducted a prospective cohort study among 20 136 eligible singleton pregnancies in 14 437 women. Information on diet, physical activity, cigarette smoking and other lifestyle factors, and anthropometric factors was collected by validated questionnaire. Gestational diabetes diagnosed by a physician was ascertained by self report and validated by medical records in a previous study.

Main results and the role of chance

During 10 years of follow-up, we identified 823 incident gestational diabetes events among the 20 136 pregnancies. Each lifestyle factor (maintaining a healthy body weight, consuming a healthy diet, exercising regularly, and not smoking) was independently and significantly associated with a lower risk of gestational diabetes. The combination of the four low risk factors was associated with a 52% lower risk compared with all other pregnancies (relative risk 0.48, 95% confidence interval 0.38 to

0.61). The population attributable risk percentage for the four risk factors in combination was 47.5% (95% confidence interval 35.6% to 56.6%).

Bias, confounding, and other reasons for caution

Well validated questionnaires were used, and the Nurses' Health Study II cohort comprises health professionals who are more familiar with health related terminology than the general population, minimizing concern for measurement errors. Moreover, measurement errors on diet and lifestyle factors are likely to be non-differential with respect to disease status and would thus have underestimated the true relative risks. In addition, we carefully controlled for major well documented risk factors for gestational diabetes to minimize confounding. Conceivably, women with classic risk factors for gestational diabetes, such as obesity and advanced age, might be screened more often for gestational diabetes than women without such risk factors, artificially increasing the observed risks associated with such characteristics. Our validation study, however, observed a high level of surveillance for gestational diabetes regardless of risk factor status and noted no significant bias in screening based on risk factor profile.

Generalizability to other populations

The relative risk estimates between lifestyle factors and gestational diabetes would be likely generalizable to other populations because the underlying biological mechanisms are likely similar. The population attributable risk percentage estimated from our cohort of health professionals, however, most likely underestimates the burden of unhealthy lifestyle on risk of gestational diabetes compared with the general population because the prevalence of these unhealthy behaviors in the Nurses' Health Study II is probably lower.

Study funding/potential competing interests

This study was supported by the intramural research program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health. The Nurses' Health Study II was funded by the National Institutes of Health and an American Diabetes Association Award.

Combined low risk lifestyle factors and risk of gestational diabetes in 20 136 pregnancies in Nurses' Health Study II

Low risk group	Percentage of pregnancies	No of pregnancies with gestational diabetes	Relative risk* (95% CI)	Population attributable risk percentage† (95% CI)
3 factors in low risk category (current non-smoker, moderate/vigorous physical activity ≥150 min/week, healthy eating‡)	20.3	112	0.59 (0.48 to 0.71)	35.4 (25.1 to 44.9)
All 4 factors in low risk category (BMI <25.0, current non-smoker, moderate/vigorous physical activity ≥150 min/week, healthy eating‡)	16.3	71	0.48 (0.38 to 0.61)	47.5 (35.6 to 56.6)

*Estimated from generalized estimating equation models and adjusted for age, parity, family history of diabetes, history of infertility, race/ethnicity, questionnaire period, total energy intake, and alcohol intake. Reference group for relative risk is all other pregnancies not in low risk group as defined in table.

†Percentage of cases of gestational diabetes in population theoretically attributable to non-adherence to particular factors.

‡Alternate Healthy Eating Index-2010 diet score in upper two fifths.

Potential benefits of minimum unit pricing for alcohol versus a ban on below cost selling in England 2014: modelling study

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STUDY QUESTION

What is the potential impact of two alcohol control policies under consideration in England: minimum unit pricing (proposed by the government in 2012) and banning below cost selling (implemented in May 2014)?

SUMMARY ANSWER

The proportion of the market affected by the two policies differs hugely, with just 0.7% of all alcohol units sold likely to be affected under a ban on below cost selling compared with 23.2% of units for a 45p minimum unit price. Below cost selling would save an estimated 14 deaths and 500 admissions to hospital annually, compared with 624 deaths and 23 700 admissions for a 45p minimum unit price.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous analyses have estimated that minimum unit pricing would be effective at reducing alcohol consumption and health harms, particularly targeted at harmful drinkers. This study found very small estimated effects for banning below cost selling and showed, in comparison, that a minimum unit price of 45p would be expected to have 40-50 times larger reductions in consumption and health harms.

Population and setting

Adults and young people aged 16 or more, including sub-groups of moderate, hazardous, and harmful drinkers, in England, 2014-15.

Design

Modelling study using the Sheffield Alcohol Policy Model (version 2.5) to compare policies of minimum unit pricing at 40p, 45p, and 50p per unit (7.9 g/10 mL) of pure alcohol with a ban on below cost selling—that is, the price of alcohol could not be lower than the tax (duty itself plus value added tax on that duty) payable on the product.

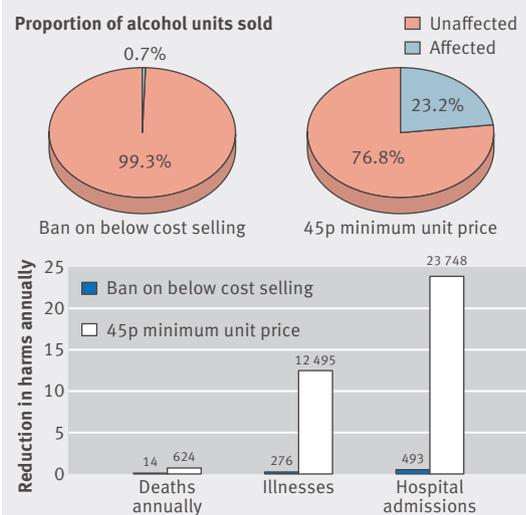
Primary outcomes

Changes in mean alcohol intake in terms of units consumed, drinkers' expenditure on alcohol, and reductions in alcohol related deaths, illnesses, admissions to hospital, and quality adjusted life years.

Main results

The proportion of the market affected is a key driver of impact. Just 0.7% of all units were estimated to be sold below the duty plus VAT threshold implied by a ban on below cost selling compared with 23.2% of units for a 45p minimum unit price. Below cost selling was estimated to reduce harmful drinkers' mean annual consumption by just 0.08%, around 3 units per year, compared with 3.7%

Estimated impact of policy to ban below cost selling compared with 45p minimum unit price on annual number of deaths, illnesses, and admissions to hospital



or 137 units per year for a 45p minimum unit price (an approximately 45 times greater effect). The ban on below cost selling has a small impact on population health—saving an estimated 14 deaths and 500 admissions to hospital annually. In contrast, a 45p minimum unit price is estimated to save 624 deaths and 23 700 admissions. Most of these harm reductions (for example, 89% of estimated deaths saved per annum) are estimated to occur in the 5.3% of people who are harmful drinkers.

Bias, confounding, and other reasons for caution

Self report surveys can have problems associated with the recording of alcohol consumption. Repeated cross sectional surveys provide estimates of the relation between changes in prices and consumption because the ideal dataset (a longitudinal panel collecting both prices paid and amounts consumed for beverage categories) is not available in the United Kingdom.

Generalisability to other populations

These results are for England but similar order of magnitude estimates are possible in Scotland, Wales, and Northern Ireland, where the ban on below cost selling is also in place.

Study funding/potential competing interests

This study was funded by a Medical Research Council and Economic and Social Research Council, UK (grant No G1000043). We have no competing interests.