Background: Persistent inflammation is proposed to contribute to various stages in the pathogenesis of CVD. Interleukin-6 receptor (IL6R) signalling propagates downstream inflammation cascades. To assess whether this pathway is causally relevant to coronary heart disease, we studied a functional genetic variant known to affect IL6R signalling.

Methods: In a collaborative meta-analysis, we studied Asp358Ala (rs2228145) in IL6R in relation to a panel of conventional risk factors and inflammation biomarkers in 125,222 participants. We also compared the frequency of Asp358Ala in 51,441 patients with coronary heart disease and in 136,226 controls. To gain insight into possible mechanisms, we assessed Asp358Ala in relation to localised gene expression and to postlipopolysaccharide stimulation of interleukin 6.

Findings: The minor allele frequency of Asp358Ala was 39 %. Asp358Ala was not associated with lipid concentrations, BP, adiposity, dysglycaemia, or smoking (p ≥ 0·04 for each). By contrast, for every copy of 358Ala inherited, mean concentration of IL6R increased by 34·3 % (95 % CI 30·4-38·2) and of interleukin 6 by 14·6 % (10·7-18·4), and mean concentration of C-reactive protein was reduced by 7·5 % (5·9-9·1) and of fibrinogen by 1·0 % (0·7-1·3). For every copy of 358Ala inherited, risk of CHD was reduced by 3·4 % (1·8-5·0). Asp358Ala was not related to IL6R mRNA levels or interleukin-6 production in monocytes.

Interpretation: Large-scale human genetic and biomarker data are consistent with a causal association between IL6R-related pathways and coronary heart disease.


Comparative Effectiveness of Weight-Loss Interventions in Clinical Practice

A randomized, controlled trial to examine effects of two behavioural weight-loss interventions in 415 obese patients with at least one CV risk factor. Participants were recruited from six primary care practices; 63.6 % women, 41.0 % black, and mean age was 54.0 years. One intervention provided patients with weight-loss support through the telephone, a study-specific Web site, and e-mail. The other intervention provided in-person support during group and individual sessions. There was also a control group in which weight loss was self-directed. Outcomes were compared between each group and control group and between the two intervention groups. The trial duration was 24 months.

RESULTS
At baseline, the mean BMI for all participants was 36.6, and the mean weight was 103.8 kg. At 24 months, the mean change in weight from baseline was −0.8 kg in the control group, −4.6 kg in the group receiving remote support only (P<0.001 for the comparison with the control group), and −5.1 kg in the group receiving in-person support (P<0.001 for the comparison with the control group). The percentage of participants who lost 5 % or more of their initial weight was 18.8 % in the control group, 38.2 % in the group receiving remote support only, and 41.4 % in the group receiving in-person support. The change in weight from baseline did not differ significantly between the two intervention groups.

CONCLUSIONS
In two behavioural interventions, one delivered with in-person support and the other delivered remotely, obese patients achieved and sustained clinically significant weight loss over a period of 24 months.

Blood pressure (BP) targets in people with diabetes are the topic of a major debate.

First evidence of BP reduction benefits in this high risk population from the UKPDS 38 trial (achieved SBP level of 144 mmHg) were further enlarged by the ADVANCE trial (achieved SBP 136 mmHg associated with significant reduction in CV and renal events, and mortality). However, recently the ACCORD clinical trial showed that lowering BP to normal levels, below currently recommended levels, did not significantly reduce the combined risk of fatal or nonfatal CVD events in adults with type 2 DM.

However, results of a recent large meta-analysis show that tight BP control is indeed associated with a lower risk of stroke in these patients; of note, this benefit occurs without concomitantly increasing the risk of myocardial infarction (MI), i.e., no “J-curve” phenomenon. Data was extracted from prospective controlled trials with a parallel design, which compared various BP-lowering agents vs. placebo or another active treatment in patients with diabetes at baseline. Overall, 31 clinical trials were included in the analysis for a total of 73,913 patients with diabetes. Stroke and MI data were extracted from 29 (corresponding to 37 arms of treatment) and 24 (corresponding to 31 arms of treatment) trials, respectively.

Overall, experimental treatment reduced the risk of stroke by 9 % (P=0.0059), and that of MI by 11 % (P=0.0015). Allocation to more-tight, compared with less-tight, BP control reduced the risk of stroke by 39 % (RR 0.61; 95 % CI, 0.48-0.79), whereas the reduction in the risk of MI did not achieve significance (odds ratio 0.87; 95 % CI, 0.74-1.02).

In a meta-regression analysis of these data, we found that the risk of stroke decreased by 13 % (95 % CI, 5-20; P<0.001) for each 5 mmHg reduction in SBP, and by 11.5 % (95 % CI, 5-17; P<0.001) for each 2 mmHg reduction in DBP.

In contrast, the risk of MI did not show an association with the extent of BP reduction (SBP, P=0.793; DBP, P=0.832). Trial sequential analysis showed that the cumulative Z-curve crossed the traditional boundary and the sequential monitoring boundaries, suggesting that firm evidence favouring tighter BP-control strategy has been reached for stroke. Considering MI as end point, the suggestion is that conclusive evidence favouring tight BP control has not been reached.

Conclusion:

The meta-analysis demonstrated that intensive BP control (below 130/80 mmHg) significantly reduces the risk of stroke, a major debilitating event in patients with diabetes and hypertension. The results also remove the potential concern for an increased risk of MI at low levels of achieved BP, as a J-curve effect was not observed down to low levels of systolic and diastolic BPs.

Therapeutic inertia (leaving patients with diabetes with BP values of 140/90 mmHg or higher) should be avoided at all costs, as this would lead to an unacceptable toll in terms of human lives, suffering, and socioeconomic costs.

*Effects of intensive BP reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. Hypertens. 2011; 29:1253-1269*
Long-Term Persistence of Hormonal Adaptations to Weight Loss

**BACKGROUND**

After weight loss, changes in the circulating levels of several peripheral hormones involved in the homeostatic regulation of body weight occur. Whether these changes are transient or persist over time may be important for an understanding of the reasons behind the high rate of weight regain after diet-induced weight loss.

**METHODS**

Fifty overweight or obese patients without diabetes were enrolled in a 10-week weight-loss program for which a very-low-energy diet was prescribed. At baseline (before weight loss), at 10 weeks (after program completion), and at 62 weeks, circulating levels of leptin, ghrelin, peptide YY, gastric inhibitory polypeptide, glucagon-like peptide 1, amylin, pancreatic polypeptide, cholecystokinin, and insulin, and subjective ratings of appetite were examined.

**RESULTS**

Weight loss (mean [±SE], 13.5 ± 0.5 kg) led to significant reductions in levels of leptin, peptide YY, cholecystokinin, insulin, and amylin, and to increases in levels of ghrelin, gastric inhibitory polypeptide, and pancreatic polypeptide. There was also a significant increase in subjective appetite. One year after the initial weight loss, there were still significant differences from baseline in the mean levels of leptin, peptide YY, cholecystokinin, insulin, ghrelin, gastric inhibitory polypeptide, and pancreatic polypeptide, as well as hunger.

**CONCLUSIONS**

One year after initial weight reduction, levels of the circulating mediators of appetite that encourage weight regain after diet-induced weight loss do not revert to the levels recorded before weight loss. Long-term strategies to counteract this change may be needed to prevent obesity relapse.

(ClinicalTrials.gov number, NCT00870259.)


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### Intensive Diabetes Therapy and Glomerular Filtration Rate in Type 1 Diabetes

An impaired glomerular filtration rate (GFR) leads to end-stage renal disease and increases the risks of CVD and death. Persons with type 1 diabetes are at high risk for kidney disease, but no interventions have proved to prevent impairment of the GFR in this population.

This Study showed that the long-term risk of an impaired GFR was significantly lower among persons treated early in the course of type 1 diabetes with intensive diabetes therapy than among those treated with conventional diabetes therapy.

(DCCT/EDIC ClinicalTrials.gov numbers, NCT00360815 & NCT00360893.)

*The DCCT/EDIC Research Group; November 12, 2011 (10.1056/NEJMoai1111732)*
**Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors**

**BACKGROUND**

Obesity in childhood is associated with increased cardiovascular risk. It is uncertain whether this risk is attenuated in persons who are overweight or obese as children, but not obese as adults.

**METHODS**

Data was analyzed from four prospective cohort studies that measured childhood and adult body-mass index (BMI, the weight in kilograms divided by the square of the height in meters). The mean length of follow-up was 23 years. To define high adiposity status, international age-specific and sex-specific BMI cut-off points for overweight and obesity were used for children, and a BMI cut-off point of 30 was used for adults.

**RESULTS**

Data were available for 6328 subjects. Subjects with consistently high adiposity status from childhood to adulthood, as compared with persons who had a normal BMI as children and were non-obese as adults, had an increased risk of type 2 diabetes (relative risk, 5.4; 95% confidence interval [CI], 3.4 to 8.5), hypertension (relative risk, 2.7; 95% CI, 2.2 to 3.3), elevated low-density lipoprotein cholesterol levels (relative risk, 1.8; 95% CI, 1.4 to 2.3), reduced high-density lipoprotein cholesterol levels (relative risk, 2.1; 95% CI, 1.8 to 2.5), elevated triglyceride levels (relative risk, 3.0; 95% CI, 2.4 to 3.8), and carotid-artery atherosclerosis (increased intima–media thickness of the carotid artery) (relative risk, 1.7; 95% CI, 1.4 to 2.2) (P≤0.002 for all comparisons).

Persons who were overweight or obese during childhood but were non-obese as adults had risks of the outcomes that were similar to those of persons who had a normal BMI consistently from childhood to adulthood (P>0.20 for all comparisons).

**CONCLUSIONS**

Overweight or obese children who were obese as adults had increased risks of type 2 diabetes, hypertension, dyslipidaemia, and carotid-artery atherosclerosis. The risks of these outcomes among overweight or obese children who became non-obese by adulthood were similar to those among persons who were never obese. (Funded by the Academy of Finland and others.)

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