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Up front

Competition for publication in *Diabetologia* continues to grow, and less than 20% of papers are accepted. Of all the high-quality papers that appear in this month's issue I want to draw your attention to five articles that I think are particularly interesting. The articles are summarised here. Our publisher, Springer, has kindly made the full text of each of these papers freely available.
I hope you enjoy reading them!

Sally M. Marshall, Editor

Combatting type 2 diabetes by turning up the heat

Patrick Schrauwen, Wouter D. van Marken Lichtenbelt

Obesity and overweight are common in our society and are associated with the development of chronic metabolic diseases, including type 2 diabetes. Weight loss can ameliorate these disorders but achieving and maintaining weight loss is difficult. Exercise does not lead to major weight loss but it is able to offset many of the obesity-associated metabolic diseases. More recently, evidence has also accumulated to suggest that breaking sedentary time by standing or walking has major health effects. Furthermore, mild cold exposure may improve metabolic health. Although the exact working mechanisms of such interventions are not yet known, in this issue Schrauwen and van Marken Lichtenbelt review how an increase in energy and substrate turnover may be involved. Energy turnover is detected at the cellular level by energy sensors, which potentially underlie the effects linking energy turnover with metabolic health. Therefore, increasing energy turnover should be considered an important strategy for the prevention and/or treatment of type 2 diabetes.

Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial

Peter Gæde, Jens Oellgaard, Bendix Carstensen, Peter Rossing, Henrik Lund-Andersen, Hans-Henrik Parving, Oluf Pedersen

In this issue, thirteen years after the end of the intensified and multifaceted intervention of the Steno-2 study, the Danish investigators, Gæde et al, report on a potential gain in years of life in participants. Originally, in 1993, 80 type 2 diabetes patients with microalbuminuria (a marker of generalised vascular damage) were randomised to healthy living, whereby patients were continually taught about healthy living whilst receiving tailored and target-driven polypharmacy of blood glucose, blood lipids, blood platelets, blood pressure and microalbuminuria. Alternatively, 80 patients were treated according to national guidelines. At conclusion of the 8 year trial, the authors previously reported a ~50% reduction of micro- and macrovascular morbidities. At this 13 years post-trial milestone, the intensively treated patients demonstrated an increase in median life span of 7.9 years and a median delay for new-onset macrovascular events of 8.1 years,

compared with those receiving conventional treatment. Thus, not only is life length increased with intensified, multifactorial treatment but it is suggested that these gained years of life are spent without major cardiovascular disorders. These findings indicate the importance of structured multifaceted interventions in type 2 diabetes care.

Maternal gestational diabetes and childhood obesity at age 9–11: results of a multinational study

Pei Zhao, Enqing Liu, Yijuan Qiao, Peter T. Katzmarzyk, Jean-Philippe Chaput, Mikael Fogelholm, William D. Johnson, Rebecca Kuriyan, Anura Kurpad, Estelle V. Lambert, Carol Maher, José A.R. Maia, Victor Matsudo, Timothy Olds, Vincent Onywera, Olga L. Sarmiento, Martyn Standage, Mark S. Tremblay, Catrine Tudor-Locke, Gang Hu, for the ISCOLE Research Group

Some studies have found that maternal gestational diabetes mellitus (GDM) places offspring at increased risk of long-term adverse outcomes, such as obesity. However, most of these studies are from high income countries, with limited data from low to middle income countries. Using a large study in 4740 children from 12 developing and developed countries around the world, in this issue Zhao et al report that the increased risk for children of GDM mothers was 53% for obesity, 73% for central obesity and 42% for high body fat, compared with those of non-GDM mothers. However, this association was not fully independent of maternal BMI. Thus, lifestyle interventions among GDM women may prevent childhood obesity in offspring.

The type 2 diabetes presumed causal variant within *TCF7L2* resides in an element that controls the expression of *ACSL5*

Qianghua Xia, Alessandra Chesi, Elisabetta Manduchi, Brian T. Johnston, Sumei Lu, Michelle E. Leonard, UrsulaW. Parlin, Eric F. Rappaport, Peng Huang, Andrew D. Wells, Gerd A. Blobel, Matthew E. Johnson, Struan F. A. Grant

Although genome wide association studies have revealed genomic locations that are robustly associated with type 2 diabetes, they do not necessarily yield the precise location of culprit genes. Given that a causal variant of type 2 diabetes has been inferred at the particularly strongly associated *TCF7L2* locus, in this issue Xia et al report on the impact of the use of clustered regularly interspaced short palindromic repeats (CRISPR) to edit out the region immediately around the relevant single-nucleotide polymorphism on global gene expression in colon-derived cells. In parallel, the authors used chromatin conformation capture approaches to identify physical contacts between this genomic region and the perturbed genes. Although *TCF7L2* expression was impacted to a certain extent, there was a strong impact on the expression of *ACSL5*, which encodes acyl-CoA synthetase long chain family, member 5. This enzyme plays a role in lipid metabolism and is known to influence insulin sensitivity, thus presenting as a putative target for further investigation. This article is the subject of a commentary in this issue by Martijn van de Bunt.

Effective endothelial cell and human pluripotent stem cell interactions generate functional insulin-producing beta cells

Dodanim Talavera-Adame, Orison O. Woolcott, Joseph Ignatius-Irudayam, Vaithilingaraja Arumugaswami, David H. Geller, Donald C. Dafoe

The ultimate goal of research into diabetes is to generate insulin-producing cells from human stem cells for transplantation into patients with diabetes to control blood glucose levels, eliminating the need for insulin injections and avoiding the progression of devastating complications. In this issue, Talavera-Adame et al report that effective interactions between human pluripotent stem cells and human dermal endothelial cells in vitro give rise to insulin-producing cells. They tested the capacity of these cells to release insulin in response to high levels of glucose in vitro, and in vivo after transplantation in an animal model of diabetes. The authors suggest that endothelial cells provide the essential signals for in vitro differentiation of human pluripotent stem cells into insulin-producing cells. In theory, stem cells could be donated by the diabetic person with a future need for a transplant for in vivo production of differentiated, insulin-producing cells. Thus, this form of 'personalised medicine' may abolish issues of transplant rejection by patients. In summary, these findings are promising for the treatment of insulin-dependent diabetes via pluripotent stem cell transplantation.