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Diabetologia

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 stand out in some regard and are very 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!

Hindrik Mulder, Editor

The 'scientist', the 'analyst' and the 'novelist': science or metrics?

Enzo Bonora

Progress in medicine relies on scientific literature because journals are the main peer-reviewed medium of discoveries, achievements, concepts and ideas, inspiring further research as well as establishing best clinical practices. In this issue, Enzo Bonora (https://doi.org/10.1007/s00125-022-05808-0) illustrates the huge increase in diabetes-related literature over the last few decades but highlights what he believes is an excess of 'nothing-to-add' papers and, in particular, redundant meta-analyses and repetitive narrative reviews. He also emphasises the enthusiasm that meta-analyses and reviews receive from some journals and some scientists, anxious to improve their own metrics. He concludes that the scientific relevance of papers and the scientific achievements of investigators and journals are more important for medical progress than their respective metrics. See the counter-debate by Deirdre Tobias in this issue.

Missing the forest-plot for the trees

Deirdre K. Tobias

Systematic reviews and meta-analyses are respectable research tools when used correctly. In this issue, Deirdre Tobias (https://doi.org/10.1007/s00125-022-05862-8) describes, however, how the quality of systematic reviews today is highly variable, despite standard operating procedures and best practices, warranting serious concerns about over-reliance on their findings without paying careful attention to potential bias. She discusses how this has undoubtedly led to some arguments against their use and value to the scientific community (see the counter-debate by Enzo Bonora in this issue). However, she goes on to highlight that dismissing this critical and growing evidence base altogether would be a disservice to rigorous scientific progress. She concludes that researchers should instead be encouraged to improve their proficiency in reading, conducting and interpreting systematic review research so that these reviews better serve their intended role as efficient synthesisers of accumulating evidence and gatekeepers of redundant original research.

Projecting the incidence and costs of major cardiovascular and kidney complications of type 2 diabetes with widespread SGLT2i and GLP-1 RA use: a cost-effectiveness analysis

Jedidiah I. Morton, Clara Marquina, Jonathan E. Shaw, Danny Liew, Kevan R. Polkinghorne, Zanfina Ademi, Dianna J. Magliano

Sodium–glucose co-transporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) reduce the incidence of cardiovascular and kidney disease in addition to their effects on blood glucose. However, it is unclear if they are cost-effective on the basis of their cardiovascular and

kidney benefits alone, which may be why many payers/governments have HbA_{1c}-based restrictions on their use. In this issue, Morton et al (https://doi.org/10.1007/s00125-022-05832-0) report that, based solely on their cardiovascular benefits at current prices, SGLT2is are cost-effective for anyone with type 2 diabetes from the Australian healthcare perspective, while GLP-1 RAs are unlikely to be cost-effective, even in a population with pre-existing cardiovascular disease. The authors conclude that these findings suggest that existing HbA_{1c}-based restrictions on SGLT2i use may not be justified from a health economic perspective.

Inequalities in cancer mortality trends in people with type 2 diabetes: 20 year population-based study in England

Suping Ling, Francesco Zaccardi, Eyad Issa, Melanie J. Davies, Kamlesh Khunti, Karen Brown

Owing to improvements in cardiovascular disease prevention and treatment in the past few decades, mortality rates in people with type 2 diabetes have declined substantially in some high-income countries. Given the increased incidence and mortality for some cancers associated with diabetes, it is unclear whether cancer has overtaken cardiovascular disease as the key cause of death in this population and whether inequalities exist in cancer mortality trends. In this issue, Ling et al (https://doi.org/10.1007/s00125-022-05854-8) report that, in contrast to declining all-cause mortality rates in people with type 2 diabetes at all ages between 1998 and 2018, there were decreasing trends in all-cancer mortality rates at younger ages but increasing trends at older ages (75+). In addition, they show that there were persistent inequalities in cancer mortality rates by gender and socioeconomic status and widening disparities by smoking status. The authors conclude that these findings highlight that cancer deserves a similar level of attention as other diabetes-related complications, such as cardiovascular disease, and that public health policies are needed to address persistent and widening inequalities.

Loss of RREB1 in pancreatic beta cells reduces cellular insulin content and affects endocrine cell gene expression

Katia K. Mattis, Nicole A. J. Krentz, Christoph Metzendorf, Fernando Abaitua, Aliya F. Spigelman, Han Sun, Jennifer M. Ikle, Swaraj Thaman, Antje K. Rottner, Austin Bautista, Eugenia Mazzaferro, Marta Perez-Alcantara, Jocelyn E. Manning Fox, Jason M. Torres, Agata Wesolowska-Andersen, Grace Z. Yu, Anubha Mahajan, Anders Larsson, Patrick E. MacDonald, Benjamin Davies, Marcel den Hoed, Anna L. Gloyn

Genome-wide association studies have identified multiple independent signals at the *RREB1* locus associated with type 2 diabetes. However, how altered expression or function of the transcription factor Ras-responsive element binding protein 1 (RREB1) influences diabetes risk was previously unknown. In this issue, Mattis and Krentz et al (https://doi.org/10.1007/s00125-022-05856-6) describe how a combination of zebrafish and human cellular models was used to identify disease-causing mechanisms at the *RREB1* locus. The authors show how RREB1 loss-of-function reduced insulin gene expression and insulin content in zebrafish as well as in human beta cell models. Transcriptomic analysis identified RREB1 as a regulator of several genes involved in beta cell development and function, including the *RFX* family of transcription factors. Consistent with these findings, the authors show how isolated islets from human carriers of *RREB1* diabetes risk alleles exhibited altered glucose-stimulated insulin secretion. The authors conclude that the genetic association of *RREB1* with type 2 diabetes is mediated, in part, by a transcriptional role for RREB1 in normal beta cell development and function.

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