

at 30, 60, and 120 minutes respectively, when compared with the reverse food order of carbohydrate followed by protein and vegetable. Postprandial insulin levels at 60 and 120 minutes were also significantly lower when protein and vegetables were consumed first.

The results suggest that the sequence of carbohydrate ingestion and food order may impact significantly on postprandial glucose and insulin levels. Authors suggested that the magnitude of the effect of food order on glucose levels is comparable to that observed with pharmaceutical agents that preferentially target postprandial glucose. Further to this, authors added that the reduced insulin levels suggested meal pattern order may improve insulin sensitivity; however, no possible mechanisms were proposed. Due to the small size of the study, interpretation of the data is greatly limited. Additionally, the follow up to only 120 minute after the start of meal consumption does not allow for understanding and observation over a longer time period. Future studies of larger sizes with longer follow up periods, control measures in place for the time to consume the foods, and that analysis mechanisms underlying the glycaemic effect of food order will provide further insight into the role of food order and the optimal timing of carbohydrate ingestion.

Antibiotic use and risk of type 2 diabetes

Mikkelsen KH, Knop FK, Frost M, Hallas J, Pottegård A. 2015. Use of antibiotics and risk of type 2 diabetes: a population-based case-control study. *J Clin Endocrinol Metab* In press doi:10.1210/jc.2015-2596.

The understanding and evidence of the interplay between human gut bacteria and nutrient metabolism has increased over recent years. Alterations in gut microbiota composition and function have been linked with metabolic disease states including obesity and type 2 diabetes mellitus (T2DM). Animal studies have also demonstrated the active role of the microbiota on several host metabolic pathways.

Antibiotics cause significant alterations in human gut microbiota with declines and increases in certain species, and may cause incomplete recovery of the initial composition in some individuals. Furthermore, studies have linked antibiotic exposure with obesity, diabetes, and glucose homeostasis disturbances. The aim of the current study was to investigate whether the use of antibiotics influences the risk of developing T2DM and subsequently assess whether the effect can be attributed to specific types of antibiotics.

The analysis was performed as a nationwide case-control study of incident cases of T2DM in Denmark between 2000 and 2012. Data was used from three sources: the Danish National Registry of Patients for outpatient disease diagnosis; the Danish National Prescription Registry for prescription drug dispensing information such as date, substance, brand name and quantity; and the Danish Person Registry for vital status.

New T2DM cases were defined by a first-ever prescription of a noninsulin glucose-lowering agent using the date of filling as the index date. Cases that had a diabetes diagnosis before the index date were excluded for consistency. Patients that were not inhabitants of Denmark at the index case or had migrated less than five years prior were also excluded, as were cases with chronic pancreatitis, pancreatic cancer, or polycystic ovary syndrome. For each case, eight randomly selected controls matched on gender and birth year were selected and assigned an index date identical to their corresponding case. Information on all systemic antibiotic use between 1995 and 2012 was obtained for the entire cohort, with antibiotics classified into narrow-spectrum or broad-spectrum and bactericidal or bacteriostatic. Antibiotic prescriptions within 6 months of index date were disregarded to avoid reverse causation bias. Exposure was quantified and classified into one of three groups according to the number of antibiotic courses before the index case: 0-1 antibiotic courses, 2-4 antibiotic courses, or ≥ 5 antibiotic courses. Data was analysed to assess for increased odds ratio (OR) of T2DM with increased level of antibiotic exposure.

In total, 170 504 cases of first incident users of glucose-lowering agents, representative of new T2DM cases, were identified and matched to 1 364 008 control persons without diabetes. Patients with T2DM redeemed on average 0.8 prescriptions of antibiotics per year compared to 0.5 prescriptions per year for the control. The OR associating T2DM with exposure to antibiotics of any type was 1.21 (95% confidence interval [CI] 1.19-1.23) and 1.53 (95% CI 1.50-1.55) with redemption of 2-4 and ≥ 5 prescriptions respectively, when compared to 0-1 prescriptions. Whilst no individual group of antibiotics was specifically associated with T2DM risk, slightly higher ORs were reported for narrow-spectrum and bactericidal types compared to broad-spectrum and bacteriostatic antibiotics. A dose-response relation between antibiotic exposure and T2DM was observed for all antibiotic groups, with the OR for T2DM increasing almost linearly with exposure. Importantly, increased use of antibiotics among T2DM patients was found after the time of diabetes onset as well as for up to 15 years before diagnosis.

As with all observational studies, the impact of bias and confounders is essential for consideration. As virtually all medical care in Denmark is provided through public health, analysis of Danish health registries allow true population-based studies and identification of all citizens commencing treatment with a noninsulin glucose-lowering agent during the study period, thus minimising bias. The index date, however, may be inaccurate or delayed. The data is limited by the exclusion of patients on insulin mono-therapy, but authors suggested this accounted for less than 5% of Danish population with T2DM. Additionally, data

was not available on anthropometric measures, blood samples, or gut microbiota composition for analysis. The role of antibiotic exposure in early life was unable to be analysed as the Danish National Prescription Registry provides data from 1995 onwards only.

This is an excellent study analysing the association of antibiotic use and risk of T2DM from a true population based study. Authors highlight there are two competing interpretations of the study findings: firstly, that patients with T2DM are more prone to infections many years before diagnosis of T2DM and thus have increase demand for antibiotics, or secondly, that antibiotics increase the risk of T2DM. Further investigation in interventional studies will provide more clarity.

Modifiable risk factors of Alzheimer's disease

Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, Zhao QF, Li JQ, Wang J, Yu JT. 2015. Meta-analysis of modifiable risk factors for Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 86:1299-1306.

Alzheimer's disease (AD) is the most common type of dementia and neurodegenerative disease with its aetiology associated with both genetic susceptibility and environmental factors. With increasing prevalence, significant healthcare associated burden, and no cure for the disease, identifying associated modifiable risk factors that may assist with strategies for prevention management is critical. The current study undertakes the most extensive and comprehensive systematic review and meta-analysis to date, to calculate the effect sizes for various modifiable risk factors for AD.

Authors searched PubMed and the Cochrane Database of Systematic Reviews for studies published in English that reported risk factors of AD from 1968 to July 2014, with search terms of "Alzheimer's disease", "dementia" and "risk factor". Studies were included if they met the following three factors: reported odds ratio (OR) or relative risk (RR) using a longitudinal cohort or retrospective case-control study design; included a study population representative of the general population; and the exposures identified as either positive or negative with diagnosis of AD are potentially modifiable. From the 16 906 articles identified from the initial search, 351 were included in the systematic review and 323 studies were included in the meta-analysis. A total of 93 factors were identified; however, data was presented only for factors in which the pooled population was relatively large (>5000) to reduce the error of estimates.

Significant positive and negative associations were found for 13 and 23 factors, respectively. No association was found for 23 other factors. Authors categorised exposures into seven groups of modifiable risk factors: pre-existing disease, biochemical exposures in serum/plasma, dietary exposures, medical exposures, lifestyle, occupational exposure and psychological conditions.

Grade I evidence was found for four medical exposures, oestrogen, statins, antihypertensive medications and non-steroidal anti-inflammatory (NSAIDs), as protective factors of AD. Four dietary exposures also met grade I level evidence as protective factors including folate, vitamin E, vitamin C and coffee. Grade I evidence was identified for one biochemical exposure (hyperhomocysteine) and one psychological condition (depression). The role of pre-existing diseases in AD proved complex with grade I evidence for frailty, carotid atherosclerosis, hypertension, low diastolic blood pressure and type 2 diabetes mellitus in the Asian population only, attributed with increased risk of AD. Other pre-existing disease such as history of arthritis, heart disease, metabolic syndrome and cancer had grade I evidence for decreasing risk of AD. Lifestyle factors were also complex with grade I evidence for low education, heavy smoking, high body mass index (BMI) in mid-life and low BMI (defined as at least <30 kg/m²) increasing risk of AD, whilst high BMI in late-life, cognitive activity, ever smoking, current smoking in the Western population, light to moderate drinking, and stress decreasing the risk of AD. No significant associations were observed for occupational exposures. Factors associated with reduced risk of AD with grade II-A evidence included a healthy dietary pattern, fish consumption, high A β 42/A β 40 ratio, high education, and physical activity whilst neuroticism and current smoking in the Asian population had grade II-A evidence for increased risk of AD.

The study provides a thorough and comprehensive review of potentially modifiable factors associated with AD that may increase or reduce its risk; however, it is limited by the inclusion of only English articles from specific databases. The nature of some factors, especially lifestyle and pre-existing disease, highlight the complexity of the disease and perhaps limitations in understanding of the roles in AD aetiology. The risk factors and protective factors identified in the meta-analysis may provide promising options for targeting preventative strategies, with future studies targeting these factors required.

CAM use in Australian women with heart disease, hypertension and diabetes

Sibbritt D, Davidson P, DiGiacomo M, Newton P, Adams J. 2015. Use of complementary and alternative medicine in women with heart disease, hypertension and diabetes (from the Australian Longitudinal Study on Women's Health. *Am J Cardiol* 115:1691-1695.

Despite a high level of complementary and alternative medicine (CAM) use in Australia, little is known about its usage in cardiovascular patients. Accordingly, authors of the present study aimed to examine conventional and CAM practitioner consultations, as well as use of self-prescribed CAM, among women diagnosed with heart disease, diabetes and/or hypertension.

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