NIHR | Oxford Biomedical Research Centre

Chronic Diseases Cluster & Theme Networking Events
26th March 2019

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O6 **Talk:** Body fat distribution and blood pressure in 10,000 adults with whole-body imaging: UK Biobank and Oxford Biobank *Debbie Malden*

O7 **Talk:** Liver fat content increases after a eucaloric diet enriched in saturated fatty acids, but is not affected by a eucaloric diet enriched in free sugars *Sion A Parry*

O8 **Talk:** Unravelling the role of the HHIP locus in body fat distribution *Andrea D van Dam*

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O17 Poster: The effect of weight-loss interventions on non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomised controlled trials. *Dimitrios A Koutoukidis*

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S3 Poster: Diurnal variation in performance on telephone cognitive screening in older subjects *Aubretia McColl*

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S5 Poster: Does season affect telephone cognitive screening performance in older subjects? *Aubretia McColl*

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Abstracts

C1
Hyperperfusion post-recanalisation is confined to infarcted tissue: a longitudinal voxel-based analysis.

James W Garrard

Abstract not available for distribution.

C2
DPP4 Inhibition Reverses the Detrimental Vascular Effects of Insulin in Human Atherosclerosis: Implications for Diabetes Treatment

Ioannis Akoumianakis[1], Laura Herdman[1], Marios Margaritis[1], Rana Sayeed[2], George Krasopoulos[2], Mario Petrou[2], Norbert Tennagels[3], Paulus Wohlfart[3], Keith M Channon[1], Charalambos Antoniades[1]

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Background: Despite the beneficial vascular effects of insulin in pre-clinical *in vitro* and *in vivo* models. Its integrated effects on the vascular wall of patients with atherosclerosis are unknown. Dipeptidyl peptidase 4 inhibitors (DPP4-i) are insulin-sensitising agents that may regulate vascular responses to insulin in humans.

Aim: We investigated the direct vascular effects of insulin in humans with atherosclerosis and the effect of DPP4 inhibition on vascular insulin signalling.

Methods: The study included 613 patients undergoing coronary bypass surgery. Vascular segments (internal mammary arteries (IMA), saphenous veins (SV)) were collected and incubated with insulin glargine active metabolite M1 (insulin), insulin degludec (DEG) and human insulin (HI) (1-100nM as stated), with or without pre-incubation with KR62436 (a DPP4-i) at 70µM. Vascular superoxide ($O_2.-$) was quantified by lucigenin chemiluminescence, while nitric oxide bioavailability was evaluated by quantifying the vasorelaxations to acetylcholine. Circulating DPP4 activity was measured in fasting serum using commercially available kits.

Results: Insulin increased NADPH oxidases-derived $O_2.-$ in vessels from non-diabetic and diabetic patients, an effect reversed in vascular segments from diabetic patients pre-treated with oral DPP4-i *in vivo* (A). In contrast, insulin reduced $O_2.-$ production in vessels of healthy mice used as controls (not shown). *Ex vivo* pre-incubation of human vessels with KR62436 reversed the effect of insulin on vascular $O_2.-$, supressing NADPH-oxidases activity (B) and improving eNOS coupling in human vessels (C). This resulted in improved endothelial function (D). This was a class effect, replicated using DEG and HI (not shown). DPP4 inhibition improved downstream insulin signalling by reducing insulin receptor substrate 1 (IRS1) phosphorylation at Ser307, a site linked to molecular insulin resistance (E). The

vascular effects of DPPIV inhibition may be regulated via AMPK, since DPP4-i increased AMPK Thr172 phosphorylation (F) while AMPK inhibition with compound C reversed the protective vascular effects of DPPIV-I (not shown).

Conclusions: We demonstrate for the first time that insulin induces oxidative stress and endothelial dysfunction in vascular segments from patients with atherosclerosis, independently of systemic insulin resistance. This is a consequence of local vascular insulin resistance and it may partially explain the inability of insulin treatment to improve cardiovascular outcomes in patients with moderately elevated blood glucose. Importantly, pre-treatment with a DPP4-i restores local insulin sensitivity modulating the vascular responses to insulin. These findings suggest that vascular sensitisation may be crucial when treating of diabetic patients in secondary prevention.

C3
Brain structure and white matter integrity are associated with cardiac function at rest and on exercise in young adults.

Wilby Williamson[a], **Adam J Lewandowski**[a,b] Francois Chouinard-Decorte[c], Mariane Bertagnolli[a,d] F Nils D Forkert[e], Elke Visser[f], Matteo Bastiani[f], Yasser Iturria-Medina[c], Jill Betts[a], Winok Lapidaire[a], Stefan Kluzek[g], David McKean[h], Odaro Huckstep[a], Henry Boardman[a,b], Jane Francis[b], Stefan Neubauer[b], Mark Jenkinson[f], Helen Dawes[i], Eleni Frangou[j], Alan Evan[c], Charlie Foster[k], Paul Leeson[a]

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Background: Age-related decline in central nuclei, cortical volumes and white matter integrity are associated with development of heart failure. Whether associations between brain structure and cardiac function are evident in young people is less clear.

Objectives: To examine relationships between thalamic volumes, cortical thickness, white matter integrity and cardiac function at rest and during exercise in young adults.

Methods: 121 participants (mean age 25±5 years, 49% female) completed cardiovascular phenotyping including cardiopulmonary exercise testing, multimodal cardiac and brain magnetic resonance imaging. A subgroup completed exercise stress echocardiograms with apical 4 chamber views.

Results: Stroke volume (5.8 ml/cm^3, 95%CI 2.4 to 9.1, p<0.001), ejection fraction, cardiac output (300 ml/cm^3, 95%CI 21 to 580, p=0.036) and global circumferential strain (-0.7/cm^3, 95%CI -0.1 to -1.2, p=0.03) associated with thalamic volume. Furthermore, ability to increase cardiac output on exercise was predicted by thalamus size (oxygen pulse at peak exercise increased 1.0 ml/beat per cm^3 increase in thalamic volume, 95%CI 0.4 to 1.6, p=0.001). Cardiac function also associated with white matter integrity and cortical thickness in the precuneus and posterior cingulate regions. These areas of cortical thickening were co-located with those associated with thalamus size and associations between white matter integrity and cardiac function were explained in mediation analysis through thalamic volume (stroke volume 4.8 ml per 0.01 FA unit increase, 95%CI 2.7 to 7.0, p<0.05).

Conclusions: There is preliminary evidence that central and cortical brain structure as well as white matter integrity associate with cardiac function in young adults. The thalamus may be a common functional pathway in these associations. To slow the trajectory of age-related declines in heart-brain axis function interventions may need to start early in life.

C4
Trends in incidence rates of acute stroke and 30-day case fatality rates in England between 1999 and 2011: a record-linkage study of over 1 million incident strokes.

Olena Seminog MD, PhD, Lucy Wright, PhD, Michael Goldacre, professor.

Background: Incidence rates of acute stroke have declined in high-income countries, but at a slower rate than mortality. There is only limited information on trends in stroke incidence rates in England, and on trends in short-term case fatality in hospitalised individuals.

Methods: A linked dataset of national routine hospital statistics and mortality was analysed to calculate trends in stroke incidence rates and 30-day case fatality rates (CFR) between 1999 and 2011. In calculations of incidence rates, the numerators were the total number of hospital admissions plus out-of-hospital deaths, and the denominators were the mid-year population estimates for relevant calendar years, expressed per 100 000. To calculate CFR we divided the total number of deaths from any cause in people admitted with stroke by the total number of stroke admissions.

Results: There were 1,030,319 acute strokes, 55% in women. Between 1999 and 2011 age-standardised incidence rates decreased in men from 320.7 per 100 000 to 220.0, and in women from 263.2 to 178.7 (Figures 1, 2). The reporting of stroke type in electronic patient records has improved: in 2011 only 15% were not classified as haemorrhagic or ischaemic stroke. There was a reduction in short-term mortality from 27% to 13% in men and from 28% to 17% in women at 30 days after hospitalisation for stroke (Figure3).

Conclusions: In the first decade of the 21st century hospitalised incidence rates from stroke decreased by a third. Trends differed depending on stroke type, due to changes in reporting of stroke type, and by age and sex. The observed increase in ischaemic stroke rates, contrasting to the overall reduction, was an artefact due to the improved recording. 30-day case fatality following stroke fell in men and women.

C5

Suboptimal Blood Pressure in Young Adults is Associated with Lower Enjoyment and Altered Systolic Performance during Moderate Intensity Physical Activity.

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Background – Exercise interventions to reduce blood pressure are ineffective long term due to low adherence. We hypothesised early myocardial changes in young adults with suboptimal blood pressure may result in an adverse physiological response to exercise that negatively impacts on their enjoyment of physical activity.

Objectives - To study whether young adults with suboptimal blood pressure have differences in cardiac and perceived response to exercise.

Methods - We studied 146 young adults (age 27±5 years) with a range of cardiovascular risk factors in whom cardiac structure and function had been assessed by cardiac magnetic resonance and echocardiography. 71 had undergone cardiopulmonary exercise testing with myocardial response to exercise assessed by echocardiography at 40%, 60%, and 80% of peak exercise load and by post-exercise plasma copeptin release. Perceived exertion during stress was evaluated on the Borg scale and general exercise perceptions by the Physical Activity Enjoyment Scale.

Results – Participants were grouped into those with systolic or diastolic blood pressure ≥ 120/80 mmHg (n=62) or blood pressure < 120/80 mmHg (n=84). Left ventricular mass indexed to end-diastolic volume (0.68±0.13 vs 0.62±0.12 g/ml, p=0.007) and longitudinal systolic strain were different at rest in those with suboptimal blood pressure. During exercise this group had a smaller increase in ejection fraction up to 40% workload (10.4±5.92 vs 19.0±6.90%, p<0.001) and achieved ejection fraction at 40% workload inversely associated with the post-exercise physiological stress marker, plasma copeptin (r^2=0.115, p=0.043). Those with suboptimal blood pressure reported greater perceived exertion at 40% workload (10.7±1.9 vs 9.60±1.90, p=0.039) and lower overall enjoyment of physical activity (56.7±9.9 vs 63.1±10.2, p = 0.017).

Conclusions - Young adults with suboptimal blood pressure report less enjoyment of physical activity and exhibit physiological differences in their cardiac stress response. Further work is required to determine whether addressing this distinct early exercise response can improve efficacy of lifestyle prevention programmes.

C6
Routine use of the Acurate Neo self-expanding TAVI valve is associated with improved procedural outcomes and reduced post-operative length of stay: insights from a single centre registry.

Rafail A. Kotronias

Abstract not available for distribution.

C7
Ultrasound guided vascular access site management and left ventricular pacing are associated with improved outcomes in contemporary transcatheter aortic valve implantation: insights from a single centre registry.

R.A. Kotronias

Abstract not available for distribution

C8
Is rotational atherectomy using the radial access safe in patients with severe aortic stenosis? A propensity matched analysis.

Rafail A. Kotronias

Abstract not available for distribution.

C9
Determinants of the decline in mortality from acute stroke in England: linked national database study of 811 029 adults.

Olena Seminog

Abstract not available for distribution.

C10
Long-term time trends in hospitalisation rates for myocardial infarction in the English population: a database study, 1968 to 2011

Lucy Wright

Abstract not available for distribution.

D1

The NIHR Oxford Biomedical Research Centre Diabetes & Metabolism Theme Core Lab

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The Diabetes & Metabolism Theme Core lab was established in 2017 to provide assistance to researchers within the Diabetes and Metabolism theme for their BRC supported studies.   The aim is to provide a centralised facility for the processing of biosamples for translational studies and to support clinical investigators who do not have their own laboratories. The lab maintains a suite of equipment available to users across the theme and for which we provide guidance, training and technical support (Maxwell nucleic acid purification/quantitation platform, Enspire multimode plate readers, QuantStudio7 real time PCR system, automatic biochemistry analyser). The current team consists of a lab manager, a research assistant and a technician.

We provide practical expertise for larger projects and those where staffing levels or timelines mean that extra support is required. The team has considerable practical experience in a broad range of techniques including nucleic acid extraction/quality control/archiving, gene expression (qRT-PCR) protein expression (immunohistochemistry, immunofluorescence, western blotting), biochemical assays and cell culture. When needed, we can offer assistance in developing pipelines, work-flows and SOPs for new assays. As part of our remit we also support the human islet isolation facility by contributing to the on-call rota, by performing quality control assays on isolated human islets prior to transplant and by distributing human islets for BRC supported research in Oxford.

Our current portfolio of projects includes collaborations with academics, industry and projects within the Innovative Medicines Initiatives.

D2
Genotype-Based Recall Studies Shed Light On The Impact of PAM Type 2 Diabetes Risk Alleles On Beta-Cell Function & Treatment Response

Mahesh M Umapathysivam

Abstract not available for distribution.

D3
The effect of Lixisenatide on post-prandial blood glucose and glucagon in type 1 diabetes

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[1]Oxford Centre for Diabetes Endocrinology and Metabolism, [2]Oxford Biomedical Research Centre, [3]Diabetes Trial Unit, Oxford, UK, [4]University of Copenhagen, Copenhagen, Denmark.

Background: The glucagon-like peptide-1 receptor agonist, Lixisenatide, suppresses glucagon and reduces hyperglycaemia in type 2 diabetes. Our aim was to investigate the impact of Lixisenatide on postprandial blood glucose and glucagon level in type 1 diabetes (T1D)

Methods: In a double blind, placebo-controlled crossover trial 25 subjects with T1D on multiple insulin injections were randomised to receive adjunctive treatment with Lixisenatide or placebo for four weeks in random order with a four-week washout in between. Continuous glucose monitoring (CGM) was performed before and at the end of each treatment period. The primary outcome was the proportion of post-prandial blood glucose (PPBG) CGM readings within 4-10 mmol/L. Participants also underwent a standardised liquid mixed meal test (MMT) and a hyperinsulinaemic hypoglycaemic clamp at the end of each treatment period to compare glucagon level in the post-prandial period and during hypoglycaemia.

Results: The mean±SE percentage of PPBG CGM readings in range was not different before and after treatment and for each meal for Lixisenatide compared with Placebo ($p=0.6-0.9$)). Mean HbA1c did not change during treatment periods. There was a reduction in total prandial insulin dose after Lixisenatide compared with Placebo (-0.7 ± 0.6 *vs.* $+2.4\pm0.7$ units/day, $p=0.004$), but the total basal insulin dose was not different between treatments.

Glucose level (mmol/l) in the MMT rose significantly less after Lixisenatide treatment than placebo: AUC at 120 mins was 392.0 ± 167.7 for Lixisenatide and $628.1+132.5$ mmol/L x min after placebo ($p<0.001$). Glucagon level (pmol/L) was suppressed post MMT in the Lixisenatide group compared to placebo ($4.5+0.5$ *vs.* $9.5+0.8$ at 120 mins, $p<0.001$, and $4.1+0.5$ *vs.* $7.7+1.0$ at 150 mins. $p=0.003$).

Glucagon, adrenaline, noradrenaline, cortisol and pancreatic polypeptide levels at a blood glucose level of 2.4 mmol/L during the hypoglycaemic clamp, were the same for Lixisenatide compared with Placebo.

Conclusion: In T1D, the proportion of PPBG values in target range were not altered by Lixisenatide compared with placebo treatment. There was a reduction in prandial insulin requirements after treatment with Lixisenatide and glucose and glucagon levels were significantly reduced after a MMT following Lixisenatide, with no evidence of altered counter-regulatory responses during hypoglycaemia. Lixisenatide treatment may be useful for some individuals with T1D in whom post-prandial hyperglycaemia is problematical.

D4
Divergent Effects On T2D Of Alleles Associated With Increased Liver Fat Reflect Differential Impact On Hepatic Glucose And Lipid Output

Robert W. Koivula[1,2], IMI-DIRECT Consortium, Paul Franks[1,2], Tue Hansen[3], Andrew Hattersley[4,5], Markku Laakso[6], Ewan Pearson[7], Femke Rutters[8], Fredrik Karpe[1], Jeremy Tomlinson[1], Leanne Hodson[1], Anubha Mahajan[9], Mark I. McCarthy[1,9,10]

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Non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2D) often coincide but the physiological relationship is unclear. Important clues are provided by human genetics: variants associated with NAFLD risk have divergent effects on T2D. At TM6SF2 the NAFLD-risk allele (rs58542926:T) predisposes to T2D whilst at *GCKR* (rs1260326:T), it protects. We hypothesize that these divergent effects result from the impact of NAFLD-raising alleles on hepatic lipid output (HLO) and hepatic glucose output (HGO) respectively.

To test this hypothesis, we applied structural equation modeling (SEM) to data from the IMI-DIRECT study, including 1350 European participants, 923 non-diabetic (C1) and 427 with recently-diagnosed T2D (C2). Insulin sensitivity (IS) was modeled from frequently sampled OGTT (C1) and mixed-meal tolerance tests (C2), and liver fat (LF) measured by MRI. SEM fit was assessed by comparing model $\chi 2$s with comparable null models: variables randomized to nodes in identical SEM definition giving comparable degrees of freedom and structure, 10,000 iterations.

The hypothesized model provided a better fit than null models (C1: $\chi 2=242$, P=0.005; C2: $\chi 2=63$, P=0.01). Decreasing HLO (via TM6SF2) was associated with an increase in LF (C1: ß=0.28 [SE 0.09], P=0.001; C2: ß=0.28 [0.12], P=0.02) and fasting plasma glucose (FG): these were mediated by LF and IS (C1: ß=0.09 [0.03], P=0.001; C2: ß=0.07 [0.03], P=0.027). Decreasing HGO (via GCKR) was not associated with LF in either cohort but was associated with a direct (non-mediated) decrease in FG (C1 only: ß=-0.08 [0.04], P=0.04).

The results support a model whereby increased genetic risk of NAFLD, arising from defects in two processes (HLO and HGO) results in opposing glycemic effects. This has important consequences for therapeutic strategies for combatting NAFLD:

approaches to reduce NAFLD through targeting of HLO (as opposed to HGO) may also reduce risk of hyperglycaemia and T2D.

D5
Liver fat content increases after a eucaloric diet enriched in saturated fatty acids, but is not affected by a eucaloric diet enriched in free sugars.

Sion A Parry[1], Fredrik Rosqvist, Thomas Cornfield[1], Pamela Dyson[1], Ferenc Mozes[2], Fredrik Karpe[1], and Leanne Hodson[1.]

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Diet has been suggested to play a key role in the pathogenesis of non-alcoholic fatty liver disease. Overfeeding fat and/or free sugars increases liver fat content; the influence of specific macronutrients, when in energy balance, is unclear. The aim of this study was to compare the effects of two eucaloric diets, one enriched in carbohydrate/free sugars and the other enriched in fat/saturated fatty acids (SFA) on liver fat content and metabolism in overweight males.

Fifteen metabolically healthy males (46.3 ± 1.2y, 27.6 ± 0.4kg/m^2) consumed a eucaloric high-fat (45% total energy (TE) as fat) diet (HF) enriched with SFA (20% TE as SFA), and a high-carbohydrate (65% TE as carbohydrate) diet (HC) enriched with free sugars (20% TE as free sugars) for 4-weeks, in random order, with a 7-week washout between diets. Liver fat content was assessed before and after each diet using magnetic resonance spectroscopy (MRS), and stable isotope tracers were used to investigate whole-body and hepatic fat metabolism in response to the diets.

Liver fat increased by 38 ± 10% following HF (from 5.3 ± 0.1% to 7.0 ± 1.3%; p=0.007), whereas the HS diet did not significantly influence liver fat (5.8 ± 1.1% and 6.1 ± 1.2% pre- and post-diet respectively; p=0.466). De novo lipogenesis (DNL) has been suggested to be a potential mediator of increased liver fat. However, when investigating fasting DNL via the incorporation of ^{2}H from heavy water (^{2}H$_2$O) in very-low density lipoprotein triglyceride (VLDL-TG) palmitate, no significant difference is evident between diets (5.9 ± 0.9% and 7.4 ± 1.8% for HF and HS, respectively; p=0.417).

Thus, preliminary findings suggest that increasing dietary intakes of free sugars when in energy balance have little effect on liver fat content, whereas consumption of an isocaloric diet enriched in fat/SFA increases liver fat. Our data also refutes the notion that increased DNL contributes to liver fat accumulation.

D6
The role of DGAT2 activity on hepatocellular and whole-body metabolism

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Background: Diacylglycerol acyltransferase (DGAT) exists as two isoforms (1 and 2) and performs the final committed step in triglyceride (TG) synthesis. In humans, DGAT2 is expressed most highly in the liver and adipose tissue. Altered function may play a role in hyperglycaemia and hyperlipidaemia, since DGAT2 primarily utilises de novo-derived substrates and contributes TG for the assembly of lipoprotein particles. However, complete in vitro knockout and human intervention data is lacking.

Methods: By using DGAT2-knockout Huh7 cells and recruiting people from the Oxford Biobank with mutations in the DGAT2 gene, along with age, sex and BMI-matched controls, the effect of altered DGAT2 activity on hepatic and whole-body metabolism was investigated. Participants underwent a postprandial study day before and after a sugar overfeeding intervention (25% energy intake) over 15-20 days.

Results: DGAT2 knockout cells displayed lower expression of carbohydrate-responsive element binding protein (ChREBP) and its target genes, markedly reduced levels of de novo lipogenesis (DNL) and a modest reduction in intracellular TG. In humans, DGAT2 mutations did not affect hepatic DNL or VLDL-TG secretion; however, they did impact substrate utilisation. Carbohydrate oxidation was significantly higher in carriers of DGAT2 mutations, whereas fat oxidation was significantly lower compared to controls. In response to a high sugar diet, differences in substrate utilisation were no longer evident between groups. Although both groups significantly increased their sugar intake, body weight and liver fat increased only in the control and not DGAT2 group.

Conclusions: Taken together, our results suggest that DGAT2 is implicated in glucose and fat metabolism through partitioning glucose towards oxidation and regulating DNL, lipoprotein secretion and liver fat accumulation. However, the complexity of how DGAT2 function may impact disease is demonstrated by the differences observed in in vitro and whole-body effects and the interaction with dietary intake, which requires further investigation.

D7
Deciphering the role of LRP5 in human adipose tissue biology and the regulation of fat distribution and systemic metabolism.

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Background and aims: Fat distribution is an independent cardiometabolic risk factor however, the molecular and cellular mechanisms regulating body shape remain obscure. WNTs are a family of stem cell growth factors signalling through the LRP5 receptor. We previously showed that subjects with gain-of-function (GOF) *LRP5* mutations had increased lower-body fat accumulation and high bone mass (HBM). Reciprocally a common low bone mineral density (BMD)-associated *LRP5* allele was associated with increased abdominal obesity. *In vitro* LRP5 knock down (KD) led to dose- and depot-specific effects on abdominal and gluteal adipose progenitor (AP) biology. *LRP5* HBM individuals also had lower fasting insulin *vs.* matched controls. Herein we set out to extend these findings by exploring the cellular and molecular mechanisms mediating the beneficial effects of LRP5 on fat distribution and systemic metabolism. We hypothesised that LRP5 promotes lower-body fat accrual and insulin sensitivity via actions in both APs and mature adipocytes and through WNT-dependent and WNT-independent signalling.

Materials and methods: (1) Adipose and metabolic phenotyping of carriers of GOF and loss-of-function (LOF) *LRP5* variants and matched controls (2) *Ex vivo* studies in fractionated adipose tissue (3) *In vitro* GOF and LOF studies in immortalised APs and differentiated adipocytes (4) RNA sequencing of induced LRP5 KD and LRP5 (wild-type and GOF) overexpressing immortalised abdominal and gluteal APs.

Results: Compared to controls (n=60) carriers of rare GOF LRP5 mutations (A242T and N198S, n=6) had lower age, sex and total fat mass-adjusted fasting glucose, fasting insulin, HOMA-IR, HOMA-B and higher adipocyte insulin sensitivity [i.e. lower (NEFA x insulin)]. GOF LRP5 mutation carriers also displayed lower android fat mass, increased leg fat mass and higher BMD. Compared to controls (n=230) carriers of a low frequency LOF LRP5 variant (V667M) displayed lower leg fat mass and reduced BMD. The area-under-the-curve for NEFA during an OGTT was lower in GOF LRP5 mutation carriers (n=6) vs. controls (n=10). In age and fat mass adjusted partial correlations from 43 females, abdominal and gluteal AP but not mature adipocyte *LRP5* gene expression correlated strongly and negatively with android-to-gynoid fat ratio. Abdominal AP *LRP5* expression also correlated positively with gynoid and leg fat mass. *In vitro*, LRP5 KD was associated with impaired abdominal and gluteal adipocyte differentiation. In preliminary experiments overexpression of LRP5 (wild-type and A242T mutant) did not modulate adipogenesis. Experiments assessing the effects of induced LRP5 KD and

overexpression on glucose uptake in mature adipocytes are ongoing. To identify the target genes and pathways through which LRP5 modulates fat distribution we have generated RNA seq data from LRP5 KD and LRP5 (wild-type and A242T mutant) overexpressing immortalised abdominal and gluteal APs. Bionformatic analysis of this dataset is ongoing.

Conclusion: Our findings provide further support that LRP5 modulates fat distribution via effects on AP biology. Our preliminary data also suggest that LRP5 positively regulates adipocyte insulin sensitivity.

Disclosure: The funders had no role in study design, analysis or reporting of the current work.

D8
Building a diabetes research registry – from aspiration to implementation

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Effective research recruitment relies on efficient access to potential volunteers. Access to linked clinical data enables feasibility assessments and enables study information to be directed to appropriate individuals. We hypothesised that a patient portal, where patients can access their own data and give consent for approach for research studies should facilitate study recruitment.

Patient input is important for such projects. We held a Patient Design Day attended by 20 people with diabetes and 10 researchers, IT experts and health care professionals. Workshops and structured discussion collated opinions on data sharing for clinical care and research and to define the key characteristics of a patient portal. Desirable features included usability, adequate data protection, linkage to other systems, features which motivate continual use and potential to upload patient's own data.

Subsequently we have worked with the OUH Trust to optimise a Diabetes patient portal linked to the Electronic patient record (EPR). Initially all those attending a diabetes outpatient appointment in OCDEM from 30 January 2019 (up to 200 individuals/month) will be eligible to register. The portal will enable patients to access their results and appointment details and allow 2-way messaging between patients and health care professionals. Standardised questionnaires will be sent electronically to patients to allow both individual and clinic-wide analysis of features such as diabetes-related distress and hypoglycaemia prevalence. Personal scores will appear in the EPR. A consent for approach for research studies will allow patients to indicate their wishes regarding contact for recruitment and linkage to data within the EPR will allow study information to be individually targeted. Feasibility searches to assess potential for recruitment will also be possible prior to commencing a study within Oxfordshire.

Initial data shows that over the first 7 days, 27 people were approached to take part, 26 agreed and 17 became active users. 1 person declined to take part due to lack of a personal computer or smartphone.

The portal will be fully evaluated to assess registration rate, subsequent use statistics and acceptability of the system, as well as rate of completion of questionnaires and research consent registration.

D9
Predicting the Risk of Hypoglycaemia in Inpatients with Diabetes

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Introduction: We analysed data obtained from inpatients with diabetes admitted to a large university hospital and predicted the risk of hypoglycaemia through the use of a number of machine learning algorithms.

Methods: We retrospectively assessed data collected from the electronic health record system at Oxford University Hospitals with the aim to predict the risk of inpatient hypoglycaemia. We extracted both laboratory and point-of-care blood glucose values to identify hypoglycaemic episodes defined as blood glucose values below 3.9 mmol/l. We predicted the risk of hypoglycaemia using information about patient demographics, administered medications, vital signs, laboratory results and procedure performed during the hospital stays. We compared 19 prediction models by contrasting their performance metrics including area under curve of the receiver operating characteristics (AUC_ROC) through a three-fold cross validation.

Results: We analysed data obtained from 17,658 in-patients with diabetes [9,277 males, age 66(18) years, mean(SD)] who underwent 32,758 admissions between July 2014 and August 2018. We identified all the hypoglycaemic episodes during these admissions and predicted the risk. The results from the logistic regression model suggested that the predictive factors of inpatient hypoglycaemia include people undergoing procedures, weight, age, type of diabetes, diastolic blood pressure, use of drugs (insulin, sulfonyurea, metformin, morphine, amitriptyline and dexamethasone) and albumin levels. The model with the best performance was the gradient boosting with AUC_ROC of 0.78 which outperforms that of the logistic regression model with AUC_ROC of 0.75.

Conclusion: Advanced machine learning models are able to predict risk of hypoglycaemia in inpatients with diabetes and can be used to support decision making when treating inpatients with diabetes.

D10
How the extended role of the Research Nurse facilitates research within the Oxford Centre for Diabetes, Endocrinology and Metabolism.

Rachel Franklin, Louise Dennis, Diana Mantripp, Sarah White

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The Clinical Research Unit (CRU), is the hub of activity for translational research within the Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), including the home of the Oxford Biobank recall studies. It is staffed by a highly experienced group of research nurses led by a nurse manager. The nurses within the unit have all had the opportunity to develop specialist skills traditionally performed by a doctor. Procedures include use of ultrasound, adipose tissue biopsies, insertion of adipose tissue microdialysis, work with stable isotopes, anthropometric measurements and Dual-energy X-ray Absorptiometry (DEXA) scans. In addition to these, some of the nurses have been trained to undertake glucose clamp procedures in studies measuring glucose metabolism, insulin secretion and insulin resistance.

This expertise has enabled efficient delivery of reliable research outcomes that positively influence and contribute to high standards of patient care, at the same time, facilitating a safe and holistic experience for research participants within the unit. This is reflected in the high levels of recruitment and retention of study participants.

In addition these unique skills have enabled the establishment of local, national and international training to assist research teams in developing these specialist techniques within their own research institutes.

The extended role of the research nurses within OCDEM facilitates world leading clinical studies within diabetes and metabolism that is making a real difference to patient care.

D11

The Oxford NIHR BioResource: A growing bioresource supporting translational studies

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The Oxford Biobank is the first Bioresource in the UK set up with the specific remit of allowing for recall studies. Participants in the Oxford Biobank are randomly recruited from the local Oxfordshire population to attend a screening visit in which a large number of data is collected from individuals. This ranges from anthropometric data, cardiovascular and diabetes risk factors, blood biochemistry and genomic data. Based on this data recall studies can be set up for defined research questions, such as recall-by-genotype or recall-by-phenotype. To date just over 9,000 30-50 year old men and women have been screened and full genomic data is available on 7,600.

More than one hundred recall studies have been completed with well over 1,000 people being recalled from a wide range of disease areas such as diabetes, obesity, cardiovascular disease, immune and inflammatory disorders, brain function.

Recall studies answer questions on functional genomics and the relevance of biomarkers in human (patho)physiology of adult chronic disease. External researchers wanting to access the facilities of the Oxford Biobank can enquire about proposals through the website www.oxfordbiobank.org.uk .

M1
Predictors of long-term risk of delirium in patients with previous TIA and stroke: prospective population-based cohort study

<u>**Sarah Pendlebury**</u>

Abstract not available for distribution.

M2
Assessing the impact of a single eGFR and e-GFR-estimating equation in the reclassification of CKD

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Nuffield Department of Primary Care Health Sciences

BACKGROUND: Chronic kidney disease (CKD) is diagnosed using estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (ACR). eGFR is calculated from serum creatinine using the MDRD or CKD-EPI equations. This study in UK primary care funded by the Oxford BRC aimed to compare the performance of one versus two eGFR/ACR measurements, and the impact of equation choice, on CKD diagnosis and classification.

METHODS: Data were used from 485 participants over 60 years old in the Oxford Renal Cohort Study who had at least two eGFR tests. The proportion of study participants diagnosed and classified into different CKD stages using a single and two positive tests were compared. Prevalence of CKD diagnosis and classification by CKD stage was compared when eGFR was calculated using the MDRD and the CKD-EPI equations.

RESULTS: Participants included in the analysis had a mean age of 72.1±6.8 years and 56.5% were female. Use of a single screening test overestimated the proportion with CKD by around 25% using either equation compared with two tests. Mean eGFR was 1.4ml/min/1.73m2 (95%CI 1.1 to 1.6) higher using the CKD-EPI equation compared with MDRD. More patients were diagnosed with CKD using MDRD than CKD-EPI (64% vs 63%, respectively), and 16 individuals with CKD stage 2-3A were re-classified as normal using CKD-EPI.

CONCLUSION: Current guidance to use two eGFR measures to diagnose CKD remain appropriate in an older primary care population to avoid overdiagnosis. A change from MDRD to CKD-EPI leads to 1 in 12 patients no longer having a diagnosis of CKD.

M3
Kidney age: development of an intervention to aid patient-doctor communication

<u>Clare Bankhead</u>

on behalf of the Kidney Age project team

BACKGROUND: Previous research confirms that the terminology "chronic kidney disease" (CKD) is problematic for both patients and general practitioners. We previously published a proposed alternative terminology "kidney age" to supersede the terminology of CKD stages 2, 3a, 3b and 4.

AIM: We aimed to develop a communication tool for use in primary care that could be the subject of a future trial.

METHOD: We used electronic health record data from UK primary care to design a prototype communication aid: a table and explanatory text showing how eGFR values map to bands of "kidney age", and the increasing CVD risk at each band of kidney age. The design and content were refined iteratively in consultation with patient-public involvement representatives. UK general practitioners were then interviewed about the proposed design and content.

RESULTS: Interviews are ongoing, but results to date suggest that GPs would welcome "kidney age" terminology and our communication tool, possibly modified, as a potential intervention.

NEXT STEPS: A web-based version of the communication aid is currently under development, for use in a future parallel-group trial.

M4
Clinical Decision-Making in Ambulatory Emergency Care

Sara McKelvie, GP & Researcher

Oxford Health NHS Foundation Trust and Nuffield Department of Primary Care Health Sciences

INTRODUCTION: Ambulatory emergency care (AEC) aims to provide hospital equivalent medical care in out-of-hospital settings with equivalent outcomes, whilst promoting patient independence and reducing the risk of hospital associated harms. There is no current training pathway for AEC clinicians and this study aims to understand the professional work of decision-making within the AEC environment. This study explores the tacit clinical practices and real-world reasoning tasks for clinicians working at the primary and secondary care interface.

METHODS: This qualitative investigation uses focused ethnography within a case study approach to explore the intellectual processes underpinning clinical decision-making in AEC.

RESULTS: Three AEC sites were purposively sampled to recruit twelve clinicians (5 GPs, 5 Consultants, 2 AEC Coordinators) and 70 hours of participant observation was complemented by 8 hours of participant interviews. Decision-Making in AEC was disseminated in time, place and person with individually-tailored plans negotiated with patients and their networks. Whilst working, clinicians frequently combined multiple roles including; triage, expert clinical advice, resource management and trainee supervision. Team interactions affected decision-making; interruptions could provide crucial information but breaks-in-task could prolong work tasks and increase cognitive load. Ten participants also worked in ED, Acute Medicine and Out-of-Hours General Practice. Participants explained how this new AEC 'community of practice' developed, and changed their clinical practice, due to the increased interaction between community and hospital based clinicians.

DISCUSSION: The findings show the intellectual challenge of AEC decision-making and how this 'community of practice' emerged from joint working at the AEC interface.

M5

Who is Integrated Care for? Methodological challenges in applied research for people with multiple long-term conditions

Caroline Potter and Ray Fitzpatrick

Health Services Research Unit, Nuffield Department of Population Health

A key output of CLAHRC Theme 3 (Patient Experience and Patient Reported Outcomes) has been the creation and testing of the Long-Term Conditions Questionnaire (LTCQ). This new patient-reported outcome measure was designed to capture what 'living well' means for people with multiple physical and/or mental health conditions, who may draw on a complex array of health and social care services.

In this presentation we describe the LTCQ's development through multiple stages of patient and stakeholder engagement, and its initial validation with a diverse sample (n=1211) of health and social care users across England. We then outline current studies testing LTCQ's potential for use in clinical practice, including monitoring patients' and carers' quality of life in local memory clinic services, and informing personalised care planning in the national Year of Care programme.

Looking forward, we will reflect on the challenges of defining and engaging the target population for applied research in multimorbidity, who are the intended beneficiaries of Integrated Care initiatives. We will then present approaches that we are pursuing to overcome these challenges, including engagement with patient and public representatives and collaboration with the Local Authority.

M6

Survival of people with valvular heart disease (OxValve-Survive)

José M. Ordóñez-Mena[1,2], Clare J Taylor[1], Andrea Roalfe[1], Joanna Wilson[2], Saul Myerson[2], Bernard Prendergast[2], FD Richard Hobbs[1]

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BACKGROUND: Valvular heart disease (VHD) occurs commonly in older patients (>65 years) but the majority is mild disease, which is of uncertain importance. Understanding the impact of VHD on mortality in this older group of patients would help determine its relevance and aid the appropriate use of healthcare resources. OxValve is a cohort study in Oxfordshire screening people aged 65 and over for VHD. Over 4,009 participants were recruited between August 2009 and May 2016 and screened using echocardiography to establish the presence and severity of VHD.

AIMS: To report survival in the OxValve cohort, and to investigate whether people with VHD are at increased risk of death.

METHODS: The OxValve cohort was linked to Office for National Statistics mortality data to obtain date and cause of death. Cox regression was used to investigate the association of any VHD, VHD of significant severity, and VHD subtypes with all-cause and cause-specific mortality, adjusting for potential confounders including age, sex, socioeconomic status, smoking, and comorbidities.

RESULTS: Linked mortality data was available for 3,511 OxValve participants up to September 2018 (median 5.85 years follow-up). VHD was present in 2,645 (75.3%) participants and of these 288 (8.2%) had significant VHD. In total, 311 (8.9%) participants had died. Cancer was the commonest cause of death (n=135), followed by cardiovascular disease (n=75) and respiratory disease (n=35). After adjustment for age and other covariates, mild to moderate VHD was not associated with increased all-cause mortality (HR 1.16, 95%CI: 0.89 to 1.50). However, VHD of significant severity (moderate or severe disease) was associated with a nearly two-fold higher risk of death overall (HR 1.92, 95%CI: 1:38 to 2.67) including increased CVD mortality (HR 2.25, 95% CI: 1.21 to 4.18).

DISCUSSION: Mild to moderate VHD was very common, but was not associated with increased mortality. Significant VHD was however associated with a two-fold reduction in survival. Further research is required to understand the natural history of VHD, how to identify those with progressive disease and when to intervene.

M7

Association between comorbidity and prescription of antihypertensives in incident hypertension: a population cohort study

Jenny Tran[1], Robyn Norton[2], Nathalie Conrad[1], **Dexter Canoy**[1,3], and Kazem Rahimi[1,3]

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BACKGROUND: Up to two-thirds of hypertensive patients have additional comorbidities. The prevalence of multimorbidity is increasing and projected to continue rising It has been suggested that the presence of comorbidity and its effects on health care provision, could also contribute to poor treatment of hypertension. It is not clear how the presence of comorbidities could affect prescriptions for antihypertensive drugs. Studies are mostly cross-sectional and have selected prevalent hypertensive patients, which limits their ability to draw conclusions about the direction of the association. To our knowledge, there are no longitudinal studies that have investigated antihypertensive prescription in people with incident diagnosis of hypertension, by presence or absence of a large number of cardiovascular and non-cardiovascular comorbidities.

PURPOSE: In patients with incident hypertension, investigate the trends and association between blood pressure treatment by number of antihypertensive medication classes and number of comorbidities, and specific comorbidities.

METHODS: We used a random 10% sample of the UK Clinical Practice Research Datalink, routinely collected electronic health records that are broadly representative of the UK in terms of age, sex and ethnicity.
We identified patients diagnosed with incident hypertension in primary care between 2000 and 2014, defined as first instance of hypertension diagnostic code in primary care. We classified antihypertensives into angiotensin-converting-enzyme (ACE)-inhibitors and angiotensin-receptor blockers, beta-blockers, calcium-channel-blockers, diuretics and other 22 comorbidities were examined, classified into six categories: cardiometabolic, respiratory, mental illness, musculoskeletal, cancer or other. We used Poisson regression landmark cohorts set annually up to 10 years after diagnosis of hypertension, to estimate the rate ratio (RR), and 95% confidence interval (CI), of number of antihypertensive classes prescribed. The exposure was number of comorbidities, specific comorbidities and disease category. We adjusted for age, sex, socioeconomic status, ethnicity, cumulative blood pressure, year of diagnosis of hypertension, baseline cholesterol, body mass index and smoking status.

RESULTS: There were 32,484 patients (51% women) with incident hypertension with mean age at diagnosis=61.6 years. The most prevalent conditions at diagnosis were arthritis (26.5%), depression (16.3%) and hyperlipidaemia (13.7%). Patients with a higher number of conditions were generally more likely to be prescribed more

classes of antihypertensive medication, and this relationship was preserved over time after diagnosis of hypertension. At 1 year after diagnosis of hypertension, patients with ≥5 or more conditions vs those with no conditions were 13% more likely to be prescribed an additional antihypertensive class compared to those with no conditions (RR 1.13 [95% CI 1.09-1.18]). Additionally, patients with cardiometabolic conditions were more likely to be prescribed an additional class of antihypertensive, and the increased RR [95% CI] remained stable over time (1 year: 1.07 [1.05-1.08], 10 years:1.08 [1.05-1.12]). However, dementia patients were less likely to be prescribed an additional class of antihypertensive class from 2 years after diagnosis (RR=0.87 [95% CI 0.76-0.99]).

CONCLUSIONS: Patients with comorbidities are generally more likely to receive antihypertensives compared to those without. This is consistent across most groups of comorbidities but tends to be more pronounced for cardiometabolic comorbidities and reversed for some conditions such as dementia. These prescribing patterns do not seem to change over time after hypertension diagnosis. An increased awareness of the impact of comorbidities on antihypertensive prescribing practices may lead to improvements in hypertension management in primary care.

Behavioural interventions to improve the quality of the grocery shopping

Carmen Piernas-Sanchez, PhD MSc, Research Fellow

Nuffield Dept. of Primary Care Health Sciences

Diet is an important determinant of health, and food purchasing is a key antecedent to consumption hence improving the nutritional quality of food purchases presents a clear opportunity to intervene. Findings from our recent systematic review of interventions implemented in grocery stores suggest that price manipulations, healthier swap suggestions, and perhaps manipulations to item availability change food purchasing and could play a role in public health strategies to improve health. However, the evidence base for interventions in grocery stores is still very limited. We are conducting a series of studies to examine the effectiveness of interventions based around healthier swaps on the quality of the food purchased and eaten as well as the short term effects on relevant health outcomes. This presentation will describe two studies to test interventions to reduce saturated fat (SFA).

In a study conducted in our experimental online supermarket we tested the effects of altering the default order of foods and/or being offered a healthier swap on the SFA content of food purchases. Compared to no intervention, altering the default order to show foods in ascending order of SFA and offering a swap with lower SFA both helped reduce the proportion of SFA in the shopping basket (-5.3% (-6.6 to -4.1 and -2.0% (-3.2 to -0.8), respectively). However, altering the default order appears a more promising way to improve food purchasing than swaps.

We have also developed a complex behavioural intervention based in primary care to improve diet quality among patients with high cholesterol (PC-SHOP study). The intervention consisted of health professional (HP) advice alone, or in combination with personalised feedback based on the nutritional analysis of grocery store loyalty card data. This trial has finished and data analysis is ongoing. Preliminary qualitative research indicated that at least half of the participants were happy about receiving healthier swaps to help them reduce the amount of SFA in their diets.

M9

Trends in survival following a diagnosis of heart failure in the United Kingdom 2000-2017: population-based study

Taylor CJ, Ordonez-Mena JM, Roalfe AK, Lay-Flurrie S, Jones NR, Marshal T, Hobbs FDR, Nuffield Dept. of Primary Care Health Sciences

OBJECTIVES: To report reliable short and long-term survival rate estimates for people with a diagnosis of heart failure and assess trends over time by year of diagnosis, hospitalisation and socioeconomic group.

DESIGN: Population-based cohort study.

SETTING: Primary Care, United Kingdom.

POPULATION: Primary care data from 55,959 patients over age 45 years with a new diagnosis of heart failure, and 278, 679 age-sex matched controls, in the Clinical Practice Research Datalink between 1st January 2000 and 31st December 2017 were linked to inpatient Hospital Episode Statistics and the Office for National Statistics civil death registry.

MAIN OUTCOME MEASURES: Survival rates at one, five and ten-years, and cause of death, for people with and without heart failure. Temporal trends in survival by year of diagnosis, hospitalisation and socioeconomic quintile.

RESULTS: Overall, one, five and ten-year survival rates increased by 6.6% (74.2% in 2000 to 80.8% in 2016), 7.2% (41.0% in 2000 to 48.2% in 2012) and 6.3% (19.8% in 2000 to 26.2% in 2007) respectively. There were 30,906 deaths in the heart failure group over the study period. Heart failure was listed on the death certificate in 13.093 (42.4%) of these patients, including 2,237 (7.2%) where it was the primary cause of death. Improvement in survival was greater for those not requiring hospitalisation around the time of diagnosis (median difference 2.4 years; 5.3 vs 2.9 years, p<0.0001). There was a deprivation gap in median survival of 2.4 years between the least and most deprived individuals (11.1 vs 8.7 years, p<0.0001).

CONCLUSIONS: Survival following a diagnosis of heart failure has shown only modest improvement in the 21st Century lagging behind other malignant conditions. New strategies to achieve timely diagnosis and treatment initiation in primary care for all socioeconomic groups should be a priority for future research and policy.

M10

Keynote speech: Discovery To Application - Digital Health in an Integrated Health System: Opportunities and Challenges

Colin McCowan

The increasing availability and subsequent use of electronic health records over the last 25 years has changed the clinical research landscape as witnessed by the growth and prominence of hitherto unheard of disciplines such as health data science and digital epidemiology. As these disciplines have matured a number of new or revised challenges have arisen which have needed new ways of working and thinking. This digital health revolution in how we do research has also facilitated new ways of feeding knowledge back into the health system to improve the service and hopefully also improve the lives of patients.

The use of EHRs to support clinical research will be illustrated using examples of digital health research undertaken over the past 25 years. The challenge of how to place the findings from research within an integrated learning health system will be highlighted using a number of current projects and initiatives. Data sharing, good governance and team data science are some of the underlying tenets required to address the challenges and opportunities raised by digital health in an integrated health system.

M11
Sensitivity of administrative hospital diagnostic coding in identifying in-hospital acute strokes complication procedures or other disease

Linxin Li, Lucy E. Binney, Samantha Carter, Sergei A. Gutnikov, Sally Beebe, Karen Bowsher-Brown, Louise E. Silver and Peter M. Rothwell.

Abstract not available for distribution.

M12
Epidemiological classification and characterisation of disease

Anthony Webster

Abstract not available for distribution.

M13
Comorbidities in the FORM-2C cohort of patients with reduced eGFR

Susannah Fleming[1], Louise Jones, Rafael Perera and **Clare Bankhead**

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PROBLEM: The FORM-2C (Frequency Of Renal Monitoring – Cystatin C and Creatinine) Study is an observational study of primary care patients with reduced eGFR (<90ml/min/1.73^2). We report comorbidity burden in FORM-2C, and how this varies in patients who discontinued the study.

APPROACH: Comorbidity data were assessed for the 747 patients in the FORM-2C cohort, across the two years of active follow-up. Diagnoses of 15 specified comorbidities (hypertension, diabetes, IHD, heart failure, MI, AF, stroke, TIA, peripheral vascular disease, thyroid disease, CKD, history of UTI, kidney stones, cancer, and prostate disorders) were noted at baseline, and updated at every study visit.

FINDINGS: The most common comorbidities at baseline were hypertension (57% of participants), established CKD (27%), and diabetes (22%). The mean number of recorded comorbidities was 2.0 (95% CI 1.9–2.1, median 2, IQR 1-3), with 59% of participants having 2 or more recorded comorbidities. Few new comorbidities were noted during follow-up, mean at 24 months was 2.2 (95% CI 2.1–2.3, median 2, IQR 1-3). The most common comorbidities noted during follow-up were history of UTI (3.9%), cancer (2.4%), CKD (1.7%), and prostate disorders (1.5%).
There were more comorbidities noted at baseline in the 59 discontinued participants (mean increase 0.21, 95% CI -0.74–0.32); however this was not statistically significant. No specific comorbidity was significantly associated with discontinuation.

CONSEQUENCES: In this elderly (mean age 70 years) cohort, there are high levels of comorbidity, despite a restricted pool being considered. We achieved good rates of follow-up which do not appear to be associated with comorbidity burden.

M14

Biological ageing based on physical and biochemical biomarkers in 0.5 million UK biobank participants

Mei Sum Chan, Matthew Arnold, Rafael Perera, Sarah Parish

The biological processes that constitute ageing and lead to age-related disease risks are poorly understood. The presence of one disease can increase the risk of another, which could represent a common biological ageing effect. Investigating biomarkers that contribute strongly to ageing in a healthy population, through estimation of a biological age, may aid disease prevention in public health.

Among 0.5 million participants aged 40-70 recruited into the UK Biobank between 2006-2010, sufficient data for this study was collected for 45 biomarkers, via physical measurement devices, blood count tests and urine tests. Touchscreen questionnaires and record linkage (≈6 years post-recruitment) provided data on prior health, secondary care outcomes and mortality. Principal Component Analysis was applied to summarise and characterise the biomarkers, and the Klemera Doubal method was used to derive a biological age for each participant by combining biomarkers strongly related to age, separately by sex and level of prior health. The predictive power of biological age for mortality and frailty was assessed, using Harrell's C-indices of adjusted Cox proportional hazards models.

Physical capability and blood pressure principal components featured most strongly, describing more than 60% (males) and 80% (females) of variation in biological age. Cognitive function, red blood cell and platelet biomarkers were next in importance. The predictive power of biological age was higher for mortality than frailty in the Healthy subset (C-index: 0.733 vs 0.653 (males), 0.699 vs 0.623 (females)). Supplementing chronological age with biological age significantly improved predictive power for mortality for all males (increase in C-index: 0.020), but not for healthy or all females (increase in C-index: <0.002), or for males in the Healthy subset (increase in C-index: 0.003).

The study identified key determinants of biological age, although the improvements of biological age over chronological age for predicting mortality and frailty were small or non-existent, based on these 45 biomarkers. However, biological age estimation in a healthier population avoided reverse causality of biomarker measurements and prior disease, and its predictive power may increase when augmented with blood plasma biomarkers in future.

M15
Prevalence of chronic kidney disease in the community: baseline characteristics from OxRen, a population-based cohort study

<u>Jennifer Hirst</u>

ABSTRACT: Chronic kidney disease (CKD) is a largely asymptomatic condition of diminished renal function and early stages of CKD may not be detected without screening. This prospective observational cohort study in UK primary care funded by the Oxford BRC aims to determine the prevalence, incidence and progression of CKD.

METHODS: Participants aged over 60 years were recruited from thirteen primary care practices in the Thames Valley. Participants with pre-existing CKD of any-stage were invited directly for the baseline assessment. Those with no previous diagnosis of CKD attended screening visits to determine whether they had an reduced estimated glomerular filtration rate, (eGFR <65ml/min/1.73m^2) or elevated albumin:creatinine ratio (ACR ≥3mg/mmol). Those with existing CKD, a single positive CKD test or two positive screening tests attended a baseline assessment (CKD cohort) to collect demographics, medical history and anthropometric measurements.

RESULTS: 3207 participants were recruited and 861 attended the baseline assessment. The CKD cohort consisted of 327 people with existing CKD, 257 people with CKD newly diagnosed through screening (CKD prevalence 18.2%), and 277 with borderline CKD (single positive test). In the 861-participant CKD cohort, 54.4% were female, mean±SD age was 74.0±6.9 years and mean eGFR was 58.1±18.4 ml/min/1.73m^2. Of the 584 with confirmed CKD, 44.0% were diagnosed through screening.

CONCLUSIONS: This study found a prevalence of CKD stages 1-5 of 18.2% in the over 60s population and around 44% of people living with CKD would remain undiagnosed without screening. Follow-up will provide data on annual incidence, rate of CKD progression, determinants of rapid progression and predictors of cardiovascular events.

M16
The Oxford consortium of prospective cohort studies in primary care (OxCoPs): development and potential applications

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BACKGROUND: Several significant long term prospective cohort studies of chronic diseases have been conducted by researchers in Oxford. These cohort studies include more than 25,000 patients and focus on vascular diseases (OxVasc), chronic kidney disease (OxRen/NewKi/Form2C), valvular heart disease (OxValve), heart failure and left ventricular systolic dysfunction (ECHOES/ECHOES-X) and transient ischaemic attack (TIA). Some of these cohorts have been recruiting participants for over 15 years and most of them are still following up patients.

AIM: With support from the Oxford Biomedical Research Centre, the researchers are collaborating to map and harmonise the data available within each cohort. This will provide a resource of high quality, collected- for- purpose data which may be analysed to answer specific research questions.

METHODS: Data from all eight cohorts have been mapped to describe the phenotypes of the included samples, the variables collected and the time frame for the data collection and follow-up period. Linkage to the Office for National Statistics and Hospital Episode Statistics will be established for all cohorts to obtain mortality data, other relevant comorbidities, and long term outcomes. For each proposed research question, the cohorts will be analysed separately and their findings will be compared and combined (if judged homogeneous enough) using meta-analytic methods.

EXPECTED APPLICATIONS: We will utilise the consortium of cohort studies to examine various predictors and outcomes of interest. Examples are: differences in the prevalence of multimorbidity and its prognosis between patients with different chronic diseases e.g. chronic kidney disease versus heart failure; the quality of life measures; indicators of frailty; and cognitive function. Bringing together these unique research studies will maximise the utility of each of the individual cohorts and provide a valuable resource for collaborative

M17

Stroke risk of patients aged 65 and over with screen-detected atrial fibrillation: collaboration and individual patient data meta-analysis

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BACKGROUND: International guidelines recommend atrial fibrillation (AF) screening for people aged 65 years and over. The stroke risk profile and eligibility for oral anticoagulation (OAC) of screen-detected AF is uncertain. We aimed to determine incidence, stroke risk (CHA2DS2-VASc), and OAC eligibility of screen-detected AF.

METHODS: Database search identified 24 AF screening studies since 2007. Authors were contacted for collaboration. We combined data for 19 studies (14 countries), in community or population screening (n = 7), general practitioner (n=6), outpatient clinics (n = 3), and pharmacies (n=3). The screening methods used were single-lead ECG (n=12), 12-lead ECG (n=4), pulse palpation (n=2), and modified blood pressure machine (n=1). Detection rate was estimated by random effects logistic regression. CHA2DS2-VASc scores were calculated using random effects Poisson regression modelling.

RESULTS: Overall 141,220 subjects were screened and 1,539 new AF cases identified. The age/sex adjusted detection rate for screen-detected AF ≥65-year-olds was 1.44% (95% CI, 1.13 to 1.82%) and 0.41% (95% CI, 0.31 to 0.53%) for <65-year-olds. CHA2DS2-VASc scores increased with age from 1.1 (<60 years) to 3.9 (≥85 years); 72% ≥65 years had ≥1 additional stroke risk factor other than age/sex. All new AF cases ≥75 years and 66% between 65-74 years had a Class-1 OAC recommendation.

CONCLUSIONS: Screening people aged 65 years and over identifies new AF in 1.4%; the majority would benefit from OAC and over 70% have at least one additional stroke risk factor other than age/sex. Our data support recommendations for AF screening commencing at age 65 years.

M18
Is statin use in chronic obstructive pulmonary disease (COPD) patients associated with lower risk of exacerbations?

Margaret Smith, Helen Ashdown, Chris Butler, James Sheppard, Clare Bankhead

PROBLEM: Some observational studies have found that statins might reduce the frequency and severity of COPD exacerbations, but a recent trial was stopped because there was no evidence of any benefit. These conflicting results may be because the trial only included patients with moderate-severe COPD and no pre-existing heart disease. However most observational studies have considered prevalent statin users and may be subject to other biases.

APPROACH: We used routinely collected data from UK primary care from the Clinical Practice Research Datalink. We extracted data on patients aged 40+ years with a previous COPD diagnosis who had not been prescribed statins in the previous year. We followed up patients for a maximum of 3-years to identify if they received a statin prescription i.e. became new-users.

We used Cox regression to calculate hazard ratios (HR) for time-to-exacerbation, severe exacerbation requiring hospitalisation, and death in new users compared to non-users of statins. Stain use was included as a binary time-dependent variable. HR were adjusted for a wide range of baseline covariates including demographic variables, covariates associated with risk of exacerbation, prescriptions for antihypertensive medication and cardiovascular comorbidities.

FINDINGS: We identified 48,124 COPD patients of whom 7270 became new-users of statins over a maximum of 3-years of follow-up. After adjustment for all covariates HR and 95% CI for outcomes in new statin-users compared to non-users were: exacerbation (1.03, 0.98-1.08); severe exacerbation (1.06, 0.98-1.15) and death (0.85, 0.77-0.94).

CONSEQUENCES: We did not find any evidence to support a beneficial effect of statin use on COPD exacerbations.

M19
Change in albuminuria and risk of renal and cardiovascular outcomes

Margaret Smith, William G Herrington, Misghina Weldegiorgis, FD Richard Hobbs, Clare Bankhead, Mark Woodward

INTRODUCTION: Changes in urinary albumin-to-creatinine ratio (UACR) may affect the risk of advanced chronic kidney disease (CKD). How much the effect depends upon natural variation and the time period for the change is unknown.

METHODS: English Clinical Practice Research Datalink records (2000-2015), with linkage to secondary care and death certification, were used to identify prospective cohorts with at least two measures of UACR within 1, 2 and 3 years. Adjusted Cox regression assessed the separate relevance of baseline UACR and UACR change to the risk of developing CKD stage 4-5 and end-stage renal disease (ESRD). Associations were compared before and after accounting for the effects of natural regression to the mean (RtM).

RESULTS: 212,810 individuals had baseline UACR measurements; 22% had a UACR ≥3.4, and 3% had UACR ≥33.9, mg/mmol. During a median 4.0 years follow-up, 5976 developed CKD stage 4-5 and 1076 developed ESRD. There were strong associations between baseline UACR and CKD stage 4-5 or ESRD risk, which doubled in strength after accounting for RtM. Over 3 years, the hazard ratios, HRs (95%CIs) for CKD stage 4-5, relative to stable UACR, were 0.62 (0.50-0.77) for at least a halving of UACR and 2.68 (2.29-3.14) for at least a doubling. Associations were weaker for shorter exposure windows (and for cardiovascular disease or death), but strengthened after allowing for RtM.

CONCLUSION: Baseline values and medium term increases in albuminuria are both associated with substantially increased risk of developing advanced CKD. Standard analyses, not allowing for RtM, may underestimate these associations.

M20
An overview of methods for early health technology assessment

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BACKGROUND: Recent years have witnessed the development of Health Technology Assessment (HTA) methods for use by developers and public bodies to assess potential cost-effectiveness at the early stages of device development.

OBJECTIVES: 1) To provide an overview of current methods used; and 2) To identify issues and needs for future key methodological development in early health technology assessment.

METHODS: Rapid review methods will be used to identify published methods papers and literature reviews related to early HTA by searching relevant electronic databases including MEDLINE, EMBASE, The National Health Services Economic evaluation database (NHS EED), the Cochrane library, and Econlit. Contacts will be made with research groups who have published early HTA work in both the UK and the Netherlands to identify relevant unpublished papers. Inclusion criteria will be research and review papers that report early HTA methods, as well as commentaries describing or discussing early HTA methods, published in English.
The overview will extract data from papers to answer the below questions:
1. How 'early HTA' was defined, especially what stage of device development means 'early'?
2. What are the proposed aims of early HTA?
3. What frameworks have been developed to evaluate early HTA?
4. What methods have been proposed/identified/applied in early HTA?
5. What are the extant methodological issues in need of further examination and development?

RESULTS: The literature review is currently ongoing and results will be ready at the time of conference in early July 2018. Initial search found four literature reviews, and five methodology development papers. Preliminary findings include that papers discussed differences between early and late stage HTA and associated methods applied. These include headroom analysis, decision analytical modelling, sensitivity analysis, Bayesian modelling, and probabilistic risk analysis. Discussions were limited on methods to identify clinical care pathways.

N1
Entrapment neuropathies: pathomechanisms and management

Annina Schmid, David Bennett

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I will provide an overview of some of our current projects, which aim to further understand the mechanisms of entrapment neuropathies and nerve repair with the ultimate goal to improve management of these patients. Using carpal tunnel decompression surgery as a model system, we have described the time course and extent of nerve regeneration and its relationship with clinical recovery and neuropathic pain. We have identified a gene that is associated with neural repair in target tissue and have explored its regenerative role in human induced pluripotent stem cell-derived sensory neurones. I will also present our recent findings on the role of inflammation in entrapment neuropathies and neuropathic pain. Finally, the outcomes of a randomised clinical trial will be shown, demonstrating that a conservative intervention including education, splinting and exercises (most likely targeted at reducing inflammation) can reduce the need for surgery in patients with carpal tunnel syndrome.

N2

NMDAR-antibody encephalitis psychopathology: systematic review and phenotypic analysis

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BACKGROUND

NMDAR-antibody encephalitis (NMDAR-Ab-E) is a potentially fatal brain disease that initially presents with psychiatric disturbance, therefore many patient initially see psychiatrists. Given that early immunotherapy improves outcomes, but given inappropriately can be harmful, clear description of psychopathology is needed to help avoid under and over-diagnosis.

METHODS

Firstly, we conducted a systematic review. A PubMed search identified a cohort of individually-reported adult patients satisfying consensus criteria for definite NMDAR-Ab-E, between 01/01/2005 and 07/10/2017. Next, an emergent list of fine-grained, lower-level features was used to collate psychopathological data, in addition to demographics and aetiology. Finally, comparisons with operationalised psychiatric syndromes and network analysis were performed with and without enrichment for reports reflecting psychiatric expertise.

RESULTS

464 individually-reported cases were included: median age was 27 years, 368/464 (79%) were female and 147/464 (32%) associated with ovarian teratoma. From 50 lower-level features, the most frequent crossed multiple traditional psychopathologic domains including psychosis, behaviour, mood, catatonia, and sleep. This pattern remained remarkably stable across demographic and aetiological subgroups (2-way ANOVA P>0·6). Network analysis confirmed that the features were closely-related and consistent between individual patients. Further modelling using PCA and information theory found that mixed mood-psychosis syndromes provided the best fit to the NMDAR-Ab-E psychiatric phases, particularly when using adequately described cases.

CONCLUSIONS

The distinctive aspect of NMDAR-Ab-E psychopathology is complexity: core aspects of mood and psychotic disorders consistently co-exist within individual patients. Alongside the predominant young female demographic, this pattern could help psychiatrists more selectively identify patients who would benefit from cerebrospinal fluid antibody testing and immunotherapies.

Deep Brain Stimulation for Multiple System Atrophy

Sean Martin [1], Tipu Aziz [1], James FitzGerald [1], Yongzhi Huang [1], Nagarajah Sarangmat [1], Marko Bogdanovic [2] and Alex Green [1]

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AIMS AND IMPORTANCE
Multiple system atrophy (MSA) is a rare form of Parkinsonism and is characterized by gait and autonomic failure. MSA symptoms are generally poorly responsive to medicines that treat Parkinson's disease.

Our aim is to assess the effects of deep brain stimulation of the pedunculopontine nucleus on autonomic and gait symptoms.

Our secondary aims are to assess the effects of stimulation on autonomic parameters, and on the movement disorder.

In addition, there is a mechanistic component looking at both peripheral autonomic activity and brain networks associated with stimulation.

METHODS
We aim to perform bilateral PPN DBS in 5-10 patients and investigate the effects of this on a variety of autonomic and gait symptoms.

We will measure autonomic and gait parameters before surgery, and again after surgery in the 'on' and 'off' stimulation conditions.

RESULTS
We have implanted 2 patients to date. We will present the preliminary data for blood pressure changes in these patients.

N4
Wearable technology in Parkinson's and REM sleep behaviour disorder

Christine Lo

Abstract not available for distribution.

N5

An update on current sleep research studies including the SCOTIA trial

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Occasional sleep problems effect about 30% of the adult population and, in 10-12%, this sleep disturbance meets clinical criteria for insomnia disorder. Impaired sleep deteriorates cognitive functioning, negatively impacts emotion regulation, and is associated with physiological consequences. The SCOTIA trial aims to investigate the impact of digital Cognitive Behavioural Therapy (CBT) for insomnia on objective markers of sleep, cortical arousal and sleep-dependent cognition. While data from subjective reports suggest that CBT is effective, the assessment of objective outcome measures, probing potential mechanistic pathways, has been neglected to date. The findings of this project will build the basis to further develop CBT and inform on health benefits associated with improved sleep. This project includes a comparative cohort of good sleepers to evaluate whether individuals with insomnia demonstrate cognitive emotional biases in attention, memory and perception, thus probing potential cognitive emotional mechanisms that may link chronic poor sleep to adverse mental health outcomes.

N6
Real time fMRI Neurofeedback for Stroke Rehabilitation

Melanie Fleming [1], Zeena Sanders [1], Catharina Zich [1], Tom Smejka [1], Marilien Marzolla [1], Cassandra Sampaio-Baptista [1], Daniel Papp [1], Sebastian Rieger [2], Heidi Johansen-Berg [1]

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Strategies to improve motor recovery after stroke are vital. Real-time fMRI neurofeedback aims to address maladaptive brain activation patterns through online feedback displayed while a patient moves their affected hand. The patient is instructed to try to alter the patterns to promote beneficial brain activity patterns. This study aims to investigate 1) whether patients can maintain increases in lateralisation of brain activity after the feedback is removed 2) whether increased lateralisation leads to improvements in upper limb function and 3) whether we can understand variability in response across patients. To date, 9 chronic stroke patients, with upper limb impairment, have been randomised to receive 3 sessions of real or sham neurofeedback. Changes in the lateralisation of brain activity are assessed using fMRI and EEG. Upper limb function is assessed using the Jebsen Taylor Test, Action Research Arm Test and the Fugl-Meyer Assessment.

N7
Discovery and Detection of Exosomal Markers for Parkinson's Disease

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INTRODUCTION
Discovery and validation of a simple blood-based biomarker for Parkinson's Disease (PD) is crucial for patient stratification and monitoring disease progression. Exosomes are circulating nanoparticles that are released by all cell types including brain cells. We hypothesized that neuronal exosomes from blood may offer a means of developing a multiplexed readout of the pathological process in PD brain.

METHODS
Immunobeads with antifouling coating using pCBMA were conjugated to the neuronal marker L1CAM to isolate neuronal exosomes. Electrochemiluminescence system was used for multiplexing. Label-free mass spectroscopy was used to profile the content of neuronal exosomes.

RESULTS
Normalised alpha-synuclein in L1CAM-positive exosomes isolated from PD serum separates patients (n=30) from healthy controls (n=30) with 79% specificity and 80% sensitivity.

CONCLUSION
Quantification of neuronal alpha-synuclein in circulating exosomes is a promising test for PD diagnostics. Further optimisation and validation of this assay may introduce a step-change in predicting or monitoring PD.

N8

Effects of age, sex and APOE genotype on hippocampal volume in the UK Biobank.

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Measurement of hippocampal volume has proven useful to track progression in several brain disorders, most notably in Alzheimer's disease (AD). For example, an objective evaluation of a patient's hippocampal volume status may provide important information that can assist diagnosis or risk stratification of AD. Here we analysed effects of age, sex, and APOE genotype on the hippocampus in 19,793 generally healthy participants in the UK Biobank. Our analyses revealed a slight but significant acceleration in the rate of hippocampal volume loss at ~62 years for females, whereas for males the rate of hippocampal volume loss increased at ~51 years. This acceleration was more prominent in carriers of two APOE e4 alleles. We present percentiles for hippocampal volume over age, which will be part of a large-scale normative database to facilitate easy determination of where an individual hippocampal volume lies within the normal distribution.

N9
Measuring short term memory with a remote tablet device.

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Memory complaints are very common in our aging society and amongst a wide range of patient groups. However, their assessment is often difficult. Patients usually need to see a doctor or psychologist, and commonly-used tests can often fail to identify mild memory impairments.

We have developed a tablet app that allows assessment of short-term memory. The test involves memorizing coloured items on a screen and identifying their shapes and location after a brief delay. An individual's overall short-term memory and rate of forgetting can be assessed, as well as various other aspects of memory function.

A validation of the app in a large sample of volunteers across a range of ages is presented. It is being piloted in patient groups. This portable assessment of memory is objective, reproducible and can be conducted by non-experts to provide an assessment memory, inside or outside of the clinic.

Cerebrovascular risk and brain structural markers of cognitive decline in ageing.

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White matter hyperintensities (WMHs) of presumed vascular origin are an important marker of vascular burden in the aging brain. WMHs are associated with impairment of attention and executive function but the relationship with cerebrovascular risk factors and structural brain changes associated with aging is difficult to disentangle. We modelled the relationship between cognition, WMHs, cerebrovascular risk factors, and indices of grey and white matter structural integrity using structural equation modelling. We analyzed data from 22059 people between 44-80 years of age from the UK Biobank. We provide evidence that a multifactorial model that includes both grey and white matter structural integrity of the frontoparietal network better explains the relationship between cognition and WMH load than a model based on WMH load as the only marker of brain health. We demonstrate that the integrity of frontoparietal networks, which are vulnerable to degeneration and vascular burden, significantly contribute to age-related cognitive impairment.

N11
Studying differences in motor learning in stroke survivors compared to healthy controls.

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Motor rehabilitation for stroke survivors is frequently informed by research of motor learning in healthy controls, however it is not fully established if stroke survivors learn motor skills in the same way, therefore potentially questioning the validity of basing rehabilitation techniques on these models. This project aims to assess motor learning in chronic stroke survivors and age-matched controls on the same task. We will also collect MRI measures of brain structure and function, TMS measures of cortical excitability and neurotransmitter systems and measures of functional impairment. These measures will allow assessment of possible predictive relationships for behavioural performance in both cohorts.

Adaptation to perturbed horizontal sound localisation cues does not impair vertical localisation: implications for training strategies in people with asymmetric hearing loss

<u>Dan Kumpik</u>

Abstract not available for distribution.

N13
Motor Recovery and Sleep after Brain Injury.

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Sleep plays an important role in consolidation of motor learning, a key component of motor rehabilitation. If sleep is impaired following brain injury, then consolidation of motor skills gained through physical rehabilitation may be suboptimal. This study aims to assess the relationship between sleep quality and motor recovery in stroke and brain injury patients. Currently 32 inpatients, 51 outpatients and 25 healthy controls have been recruited. Sleep quality was assessed objectively using actigraphy and subjectively using the Sleep Condition Indicator and a sleep diary. Patients also completed assessments of motor function (Action Research Arm test and Fugl Meyer assessment). Inpatients completed up to 3 assessments over the rehabilitation period whereas outpatients and healthy controls completed one assessment. Sleep quality will be compared between patient groups and controls and inpatient motor performance will also be analysed to look at how sleep affects motor recovery.

N14

Human Centric Drug Discovery Using a Real Word Dataset and iPSC-based Assays.

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Human Centric Drug Discovery combines primary care electronic health care records (EHR), molecular transcriptomic models and iPSC-based assays, to isolate potential drug targets for the treatment of disease.

We have developed a real-time EHR database management system and statistical software package for bespoke longitudinal retrospective studies of disease from primary care records. We have established human iPSC-based assay, capable of detecting the activity of diverse chemical compounds that modulate neuronal excitability and synaptic function while maintaining a high level of throughput for drug screening.

EHR and human *in vitro* cellular models would help the investigation of pain mechanisms, to identify drug targets and by incorporating them at the early stage would reduce the risk of late-stage clinical failure and accelerate the development of novel and effective pain therapies.

N15
Stratifying genetic risk in MS patients.

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Large-scale studies to identify the genetic risk factors that contribute to the risk of multiple sclerosis (MS) has identified over 97 genomic regions conferring disease risk, where 49 regions are unique to MS. Outwardly, it appears that the dominant contribution of genetic risk lies within the immune compartment, however, only a handful of disease risk factors have been fully characterised, resulting in the majority of autoimmune-vulnerable genomic regions remaining largely unchartered.

The apparent disparity between patients when monitoring their disease course, pathology, and highly variable response to treatments, implies that the root cause of disease between individuals may not be shared. Using ATAC-sequencing of immune cell subsets, we show that the lack of disease concordance between patients may be due to a division between the offending cell population(s) driving the disease. In identifying those cells responsible on a per patient basis, we strive towards a new avenue of precision medicine.

Properties of neural oscillations in the human pedunculopontine nucleus during anaesthesia and sleep.

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The pedunculopontine nucleus is part of the reticular activating system and has been implicated in regulating arousal states. To advance our understanding of the neuronal mechanisms of altering states of consciousness and the role of pedunculopontine nucleus in it, here we analyzed electrophysiological activities recorded from the pedunculopontine nucleus and cortex in a patient. We performed local field potentials and electroencephalogram recordings simultaneously in two experiments, one during induction of general anesthesia, and the other during natural sleep. Delta power and alpha power in the pedunculopontine nucleus appeared to increase during induction of anesthesia. Peak frequency of the induced alpha oscillations was distinctly different with alpha oscillations at awake state. Delta and alpha oscillations induced by anesthetics were synchronized between the pedunculopontine nucleus and cortex. In contrast, we also showed that deep sleep induced delta power increase in the pedunculopontine nucleus and this oscillation were coherent with it in the cortex. These studies suggest that general anesthesia is neurophysiologically distinct from natural sleep, and provide electrophysiological evidence that pedunculopontine nuclei is involved in the process of altered states of consciousness.

N17
Age-related decline in motor cortical GABA promotes retention of sensorimotor adaptation.

Gershon Spitz

Abstract not available for distribution.

O1

The impact of the announcement and implementation of the UK Soft Drinks Industry Levy on sugar content of soft drinks in the UK, 2015-18: controlled interrupted time series analysis

Peter Scarborough, Vyas Adhikari, Richard A Harrington, Ahmed Elhussein, Adam Briggs, Mike Rayner, Jean Adams, Steven Cummins, Tarra Penney, Martin White

Objectives: To measure the impact of the announcement and implementation of the UK Soft Drinks Industry Levy (SDIL) on the sugar content of soft drinks in the UK.

Design: Interrupted time series with separate models comparing time trends before and after the SDIL for eligible and exempt (control) soft drinks.

Setting: Four major UK supermarkets, August 2015 – September 2018.

Participants: 44,885 observations of soft drinks eligible for the SDIL and 32,977 observations of SDIL-exempt soft drinks over 38 monthly time points.

Interventions: The SDIL charges manufacturers and importers on the basis of sugar content of the drinks they sell at £0.18 per litre for drinks with 5-<8g sugar per 100ml, and £0.24 per litre for higher sugar content. Fruit juices and milk-based drinks are exempt. We consider two intervention points: (i) announcement of the SDIL on 16th March 2016, and (ii) implementation of the SDIL on 6th April 2018.

Main outcome measures: Change in the proportion of soft drinks over each levy threshold at both the announcement and implementation of the SDIL.

Results: For eligible drinks, compared with pre-existing trends in the proportion of drinks over each levy threshold before the announcement of the SDIL, downward trends accelerated after the announcement ($p<0.001$), and a large downward step change was observed around the point of implementation ($p < 0.05$). Downward trends post-implementation were steeper than seen pre-announcement ($p < 0.05$). Extrapolation of pre-announcement trends predicts that the proportion of eligible drinks with sugar levels higher than 5g per 100ml in September 2018 was 20 percentage points lower than if the SDIL had not been introduced. Control models showed no significant changes in level or slope post-announcement or implementation, compared to pre-announcement trends.

Conclusions: There is strong evidence that the SDIL has incentivised some manufacturers to reduce sugar in soft drinks. This could lead to reduced exposure to liquid sugars in the population, which has important health benefits.

Regulating health and nutrition claims in the UK using a nutrient profile model: A modelled health impact assessment

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Background: Health-related claims (HRCs) are statements found on food packets that convey the nutritional quality of a food (nutrition claims) and/or its impact on a health outcome (health claims). The EU stated that HRCs should be regulated such that they can only appear on foods that meet a specified nutrient profile (NP). A NP model has been proposed, but not agreed by the European Commission.

Methods: To model the impact of HRCs on health impacts in the UK, we built a front-end model to a pre-established non-communicable-disease (NCD) scenario model, the Preventable Risk Integrated ModEl (PRIME) by combining data from a meta-analysis examining the impact of HRCs on dietary choices and a survey of pre-packaged foods examining the prevalence of HRCs and the nutritional quality of foods that carry them. These data are used to model the impact of regulating HRCs on the nutritional quality of the diet and PRIME is used to model the health outcomes associated with these changes. Two scenarios are modelled: regulating HRCs with a NP model (the FSANZ NPSC and a draft EU model) so that only foods that pass the model are eligible to carry HRCs, and reformulating HRC-carrying foods that fail the model.

Results: Regulating the use of HRCs with a NP model (the FSANZ NPSC) would have unclear impacts on population health and could potentially lead to less healthy diets. This is because HRCs are currently more likely to be found on products with a better nutritional profile and restricting their use could shift consumers to less healthy diets. 258 additional deaths (95% Uncertainty Intervals [UI] -6509, 8706) were predicted if foods did not change in their nutrient composition. If all foods that currently carry HRCs were reformulated to meet the NP model criteria then there would be a positive impact of using the model: (4374 deaths averted (95%UI -2569, 14009)). The largest contributor to the uncertainty is the underpowered estimates of nutritional quality of foods with and without claims.

Conclusions: Regulating HRCs could result in negative health impacts, however the wide uncertainty intervals from this analysis demonstrate that a larger health impact assessment is necessary.

O3

Effectiveness of interventions to reduce the saturated fat content of food purchases: a factorial randomised controlled trial in an experimental online supermarket

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Background: Interventions to reduce the saturated fat (SFA) content of food purchases may help reduce consumption and lower cardiovascular risk. This factorial RCT aimed to examine the effect of altering the default order of foods and being offered a swap on the SFA content of food purchases during an online shopping experiment.

Methods: UK adults who were the primary grocery shoppers for their household were recruited online and invited to select items in a bespoke experimental online supermarket using a 10-item shopping list. Participants were randomly allocated to one of four groups (i) to see products within a category ranked in ascending order of SFA content (ii) receive an offer to swap to a product with less SFA, (iii) a combination of both interventions, or (iv) no intervention. The primary outcome was the difference in percentage energy from SFA in the shopping basket between any of the four groups. The outcome assessors and statistician were blinded to intervention allocation.

Results: Between March and July 2018, 1240 participants were evenly randomised and 1088 who completed the task were analysed (88%). Participants were 65% female and aged 38y (SD 12). Compared with no intervention (n=275) where the percentage energy from SFA was 24.8% (SD 5.0%), altering the order of foods (n=261) reduced SFA by [mean difference (95%CI)] -5.3% (-6.5 to -4.1)) and offering swaps (n=279) by -2.0% (-3.2 to -0.8). The combined intervention (n=273) was significantly more effective than swaps alone (-4.2% (-5.4 to -3.0)) but not different than altering the order alone (-0.9% (-2.1 to 0.3), p=0.11 for interaction).

Conclusions: Altering the default order to show foods in ascending order of SFA and offering a swap with lower SFA reduced percentage energy from SFA. Altering the default order appears a more promising way to improve food purchasing than swaps.

Trial registration: ISRCTN13729526 https://doi.org/10.1186/ISRCTN13729526

O4

Is doctoral referral to a low-energy total diet replacement programme cost-effective for the routine treatment of obesity?

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Introduction: In a randomised trial (DROPLET), a total diet replacement (TDR) programme reduced weight in adults who were obese by 7.2 kg at 12 months compared to a nurse-led behavioural support programme. The cost-effectiveness of this treatment is unknown.

Methods: We used a multi-state lifetable model (PRIMEtime-CE) to estimate the life-years, quality-adjusted life-years (QALYs), and healthcare costs (in UK 2017 prices) incurred over a person's lifetime for each intervention under different weight regain scenarios. We estimated incremental cost-effectiveness ratios (ICERs) for TDR versus nurse-led support, and compared estimates to a threshold of £20,000 per QALY. Total intervention costs were estimated at £34 for the nurse-led programme and £796 for the TDR programme. Costs were estimated from a healthcare perspective, and both costs and health outcomes were discounted at 1.5% per year. ICERs were calculated within subgroups defined by sex, age, and body mass index (BMI) category.

Results: Across DROPLET participants, TDR is cost-effectiveness compared to nurse-led support with an ICER of £12,955 under the assumption that weight returns to baseline at 5 years following the intervention, and £3,203 assuming that a 1kg loss in weight is maintained after 5 years following TDR. Assuming full weight regain, ICERs are lower for older adults and those with higher baseline BMI.

Conclusions: TDR is a cost-effective treatment under reasonable assumptions about weight regain after 12 months, particularly among older adults, and those with a higher starting BMI.

O5
The association of body composition with fatal and non-fatal cardiovascular outcomes from hospital records in the UK Biobank

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Introduction: Obesity, usu ally assessed as the body mass index (BMI) is a risk factor for cardiovascular disease (CVD), but raised BMI does not differentiate between muscle and fat tissue. There is uncertainty about the relative contribution of skeletal muscle mass (SMM) and fat mass (FM) to CVD outcomes.

Methods: We includ ed 367,168 participants from the UK Biobank study, recruited in 2006/10 with measures of weight, height and body composition by bioelectrical impedance. All were of white ethnicity, with no prior disease likely to affect body composition. Appendicular SMM index (ASMI, SMM in limbs divided by height2) and FM index (FMI, whole-body FM divided by height2) were calculated. Participants were followed via record linkage with NHS hospital episode statistics to ascertain fatal and non-fatal CVD outcomes including coronary heart disease, congestive heart failure and stroke. The primary analysis consisted of sex-specific Cox regression models to estimate the shape and strength of the association of quintiles of FMI and ASMI with CVD risk after adjusting for socio-demographic and lifestyle factors, medical history, FM (ASMI models only) and SMM (FMI models only) to yield hazard ratios (HR) and 95% confidence intervals (CI). Subsidiary analyses assessed the association of body-composition groups with CVD risk. These groups "low muscle/low fat", "low muscle/high fat", "high muscle/low fat", "high muscle/high fat" were defined using sex-specific median ASMI and FMI.

Results: There were 6,232 and 2,733 cases of all fatal and non-fatal CVD in males and females respectively after a median follow-up of 6 years. FMI was positively associated with CVD with extreme quintiles of FMI yielding adjusted HRs of 1.79 (95% CI 1.67-1.91) in males and 1.49 (95% CI 1.33-1.66) in females. ASMI was inversely associated with CVD risk. Compared to participants classified as "high muscle/low fat" (mean BMI: male 27 kg/m2, female 25 kg/m2) all other groups were associated with a greater CVD risk. "Low muscle/low fat" (mean BMI: male 24 kg/m2, female 23 kg/m2) was associated with an increased risk in males HR 1.22, 95% CI 1.17-1.28 but not in females HR 1.04, 95% CI 0.97-1.12. "High muscle/high fat" (mean BMI: male 32 kg/m2, female 31 kg/m2) had HR 1.33, 95% CI 1.28-1.38 in males and HR 1.16, 95% CI 1.09-1.23 in females. Finally, those associated with the highest risk had "low muscle/high fat" (mean BMI: male 27 kg/m2, female 26 kg/m2) with HR 1.58, 95% CI 1.49-1.69 in males and HR 1.34, 95% CI 1.22-1.47 in females.

Conclusion: Higher FMI was associated with a greater risk of CVD, whilst higher ASMI was associated with a lower risk of CVD. These results show the value of specific measures of body composition to identify people at increased risk of CVD.

O6

Body fat distribution and blood pressure in 10,000 adults with whole-body imaging: UK Biobank and Oxford Biobank

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Objective: To quantify the associations of regional fat mass and fat-free mass to systolic blood pressure (SBP).

Methods: This analysis combined individual participant data from two large-scale imaging studies: UK Biobank and Oxford Biobank. In both studies, participants were interviewed, measured and underwent dual-energy X-ray absorptiometry (DXA) imaging. Linear regression was used to relate SBP to anthropometric measures of adiposity (BMI, waist circumference [WC] and waist-to-hip ratio [WHR]) and DXA-derived measures of body composition (visceral android fat, subcutaneous android fat, subcutaneous gynoid fat and fat-free mass).

Results: Among 10,260 participants (mean age 49, 96% white), SBP was positively associated with visceral android fat (3.2 mmHg per SD in men, 2.8 mmHg in women) and fat-free mass (1.92 mmHg in men, 1.64 mmHg in women), but there was no evidence of an association with subcutaneous android or gynoid fat. Associations of SBP with BMI were slightly steeper than with WC or WHR; these associations remained unchanged following adjustment for fat-free mass, but adjustment for visceral android fat eliminated associations with WC and WHR, and more than halved associations with BMI.

Conclusions: This analysis indicates that visceral fat is the primary etiological component of excess adiposity underlying the development of adiposity-related hypertension.

O7

Liver fat content increases after a eucaloric diet enriched in saturated fatty acids, but is not affected by a eucaloric diet enriched in free sugars.

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Diet has been suggested to play a key role in the pathogenesis of non-alcoholic fatty liver disease. Overfeeding fat and/or free sugars increases liver fat content; the influence of specific macronutrients, when in energy balance, is unclear. The aim of this study was to compare the effects of two eucaloric diets, one enriched in carbohydrate/free sugars and the other enriched in fat/saturated fatty acids (SFA) on liver fat content and metabolism in overweight males.

Fifteen metabolically healthy males (46.3 ± 1.2y, 27.6 ± 0.4kg/m^2) consumed a eucaloric high-fat (45% total energy (TE) as fat) diet (HF) enriched with SFA (20% TE as SFA), and a high-carbohydrate (65% TE as carbohydrate) diet (HC) enriched with free sugars (20% TE as free sugars) for 4-weeks, in random order, with a 7-week washout between diets. Liver fat content was assessed before and after each diet using magnetic resonance spectroscopy (MRS), and stable isotope tracers were used to investigate whole-body and hepatic fat metabolism in response to the diets.

Liver fat increased by 38 ± 10% following HF (from 5.3 ± 0.1% to 7.0 ± 1.3%; p=0.007), whereas the HS diet did not significantly influence liver fat (5.8 ± 1.1% and 6.1 ± 1.2% pre- and post-diet respectively; p=0.466). De novo lipogenesis (DNL) has been suggested to be a potential mediator of increased liver fat. However, when investigating fasting DNL via the incorporation of ^{2}H from heavy water (^{2}H$_2$O) in very-low density lipoprotein triglyceride (VLDL-TG) palmitate, no significant difference is evident between diets (5.9 ± 0.9% and 7.4 ± 1.8% for HF and HS, respectively; p=0.417).

Thus, preliminary findings suggest that increasing dietary intakes of free sugars when in energy balance have little effect on liver fat content, whereas consumption of an isocaloric diet enriched in fat/SFA increases liver fat. Our data also refutes the notion that increased DNL contributes to liver fat accumulation.

O8
Unravelling the role of the HHIP locus in body fat distribution

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Background: The distribution of fat is an important determinant of metabolic health; whilst upper body fat accumulation is associated with an increased risk of type 2 diabetes and cardiovascular disease, gluteofemoral fat distribution protects against obesity-related disorders. Recent GWAS meta-analyses revealed that at least 2 independent signals at the hedgehog interacting protein (HHIP) locus (rs1812175 and rs13146972) are strongly associated with lower body fat distribution. HHIP is a surface receptor that negatively regulates the hedgehog signalling pathway, a pathway that strongly inhibits adipogenesis. Our aim was to unravel the molecular and cellular mechanisms by which variants at the HHIP locus modulate lower body fat accrual.

Methods: Gene expression studies in fractionated adipose tissue of subjects from the Oxford Biobank and *in vitro* functional studies in depot-specific immortalised human adipose progenitor (AP) cells.

Results: The linkage disequilibrium block containing rs1812175 and rs13146972 lies within a topologically associated domain containing HHIP, HHIP-AS1, ANAPC10, and ABCE1. EQTL data from GTEX shows that rs1812175 and rs13146972 are nominally associated with HHIP and HHIP-AS1 but not ANAPC10 and ABCE1 expression in tibial artery. HHIP and HHIP-AS1 expression was low in whole adipose tissue. In fractionated abdominal and gluteal adipose tissue, HHIP and HHIP-AS1 were more highly expressed in APs and endothelial cells compared with mature adipocytes. Both genes were also more highly expressed in gluteal versus abdominal APs and in male compared to female APs. In APs derived from both the abdominal and gluteal depot, expression of HHIP and HHIP-AS1 were highly and positively correlated, which may indicate that their expression is interrelated. In abdominal and gluteal-derived immortalised APs, HHIP and HHIP-AS1 mRNA levels were highest prior to the onset of differentiation (day 0) and declined to almost undetectable levels after 1 day of differentiation. Overexpression of HHIP and HHIP-AS1 inhibited lipid accumulation in gluteal adipocytes.

Conclusion: Our preliminary data highlight a possible role for HHIP, HHIP-AS1 and hedgehog signalling in the regulation of fat distribution, through effects on APs and/or endothelial cells.

O9

Dietary approaches to the management of type 2 diabetes (DIAMOND): interim results for a randomised feasibility trial

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Background: Some clinicians have observed that low-carbohydrate, low-energy diets can improve blood glucose control, with reports of remission from type 2 diabetes in some patients. Existing clinical trials show that low carbohydrate approaches lead to minor or no improvements in glycaemic control over higher carbohydrate weight loss programmes in the longer term. However, adherence to the diets in these studies was often poor. To improve dietary adherence and allow delivery by generalists in primary care we developed the DIAMOND programme and tested the feasibility of uptake of the programme, follow-up, and programme delivery (primary outcomes) and the impact on short-term clinical outcomes.

Methods: Patients with type 2 diabetes and BMI≥30kg/m^2 in three general practices were randomised 2:1 intervention or control (usual care) and followed up at 12 weeks. The intervention diet comprised eight weeks of a food-based diet estimated to provide 800kcal per day, excluding all foods that contain significant amounts of carbohydrate, thereafter progressing to a low-carbohydrate diet intended to meet energy needs for weight maintenance, for a further 4 weeks. This programme was delivered by practice nurses, who also offered support and motivation, and advice on goal-setting and self-monitoring, across four appointments, and provided a self-help booklet with dietary principles, recipes, shopping lists, and other behavioural support.

Results: 33 patients were randomised. The mean age of study participants was 67 years (SD 11 years; range 34-83 years), with a mean baseline weight of 101kg (SD 15.6kg, range 76-134kg). 55% of participants were female, and 94% of white British ethnicity. In an interim analysis, 100% (n=20; 95% CI 83.9-100%) of patients randomised to the intervention group attempted to undertake the dietary intervention after randomisation. 97% (n=31; 95% CI 84.3-99.5%) of participants attended the final follow up session. Mean weight loss in the intervention group was 9.9kg (SD 5.2, range 1.4-26.8kg), compared to 1.9kg (SD 2.6kg, range -2.2 to 5.7kg) in the control group. Mean reduction in HbA1c in the intervention group was 16.5mmol/mol (SD 13.6mmol/mol, -3 to 52mmol/mol), compared to 0.3mmol/mol (SD 3.1mmol/mol, range -6 to 4mmol/mol) in the control group.

Conclusions: The study will complete in January 2019, after which final analysis of outcome variables will be undertaken and will be available by the time of this conference. Feasibility will be evaluated against the pre-specified progression criteria, that 95% confidence intervals do not cross the following proportions: that 60% of intervention group participants attempt the dietary intervention, 60% of participants attend the final follow-up session, and intervention sessions are conducted with at least 60% of essential elements present. If the study meets these criteria, we will refine the intervention based on participant and practitioner feedback

and qualitative interviews, and plan a definitive trial to test the long-term effectiveness of the DIAMOND programme in improving glycaemic control in people with type 2 diabetes and obesity in primary care.

O10

Are primary-care brief interventions for obesity effective when patients are asked to pay for the treatment? A two-arm randomised trial.

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Background: A previous trial tested the effectiveness of GPs' opportunistic brief behavioural interventions which aimed to offer patients with obesity a free referral to a 12-week commercial weight loss programme. The trial showed that 77% of patients accepted and 40% attended the programme. However, GPs are unable to make free referrals in many areas but could recommend weight loss programmes at the patients' expense. This trial assessed acceptance and attendance at the weight loss programme when the patient was asked to pay.

Methods: Patients who consulted two GPs in Birmingham were screened for obesity. Individuals were enrolled if they were aged at least 18 years and had a body-mass index of at least 30kg/m² (or at least 25kg/m² if of Asian ethnicity). At the end of the consultation, in a 30-second intervention, the physician endorsed behavioural weight-management programmes as an effective way to lose weight and motivated participants to attend using similar methods to the previous trial [1]; the only difference related to the cost of the programme. In the present trial, participants were randomised to two groups where the cost of the programme was described in one of two ways. In one group ('basic cost'), the physician told the participant how much the programme cost per class. In the other intervention group ('cost-comparison'), the physician compared the programme cost to everyday discretionary purchases (i.e. cups of coffee). If participants accepted the doctor's referral they were given information about local programmes and asked to select a class that was most convenient for them. Immediately after the appointment a researcher asked participants to complete two 5-point rating scales asking whether the intervention was helpful/unhelpful and appropriate/inappropriate. A researcher telephoned participants approximately 3 weeks later to ask if they had attended the programme (primary outcome) and to seek more detailed views about the intervention using semi-structured interviews.

Findings: Sixty participants were enrolled and evenly allocated to the two groups. Overall, 28/60 (47%) participants accepted the referral, which was significantly less than when the programme was offered for free (77%, $p<0.0001$ for difference in proportions). 15/30 (50%) in the 'basic-cost' group and 13/30 (43%) in the 'cost-comparison' group, difference 6.7% (95%CI, -17.6 to 29.9). The majority of participants found the physicians intervention 'helpful' and 'appropriate' immediately after the consultation (M=4.04, SD = 0.92), however these scores were significantly less than when the programme was offered for free ($p=0.004$). 1/60 (2%) attended the weight loss programme, significantly less than when the programme was offered for free (40%, $p<0.0001$ for difference in proportions).

Conclusion: GP referral to a weight loss programme that requires patients to pay rather than offering an NHS-funded programme lowers agreement to attend and

leads to almost no attendance, even though it is acceptable. There was no evidence that comparing the cost to discretionary purchases made a difference. NHS funding to support weight loss appears crucial to successful GP opportunistic brief interventions.

Publication: Aveyard, P et al. Screening and brief intervetnon for obesity in primary care: a parallel, two-arm, randomized trial. Lancet 338, 2492-2500 (2016).

O11
A systematic review and thematic synthesis of qualitative studies exploring GP and nurses' perspectives on discussing weight with patients with overweight and obesity in primary care.

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Background: Guidelines and evidence suggest primary care clinicians should give opportunistic interventions to motivate weight loss but these are rare in practice. We sought to examine why by systematically reviewing qualitative research examining general practitioners'(GPs) and nurses' views of discussing weight with patients.

Methods: We systematically searched English language publications (1945-2018) to identify qualitative interview and focus group studies. Thematic methods were used to synthesise the findings from these papers. We synthesised the studies by identifying second-order themes (explanations offered by the original researchers) and third-order constructs (new explanations which went beyond those in the original publications). Quality assessment using The Joanna Briggs method was undertaken.

Findings: We identified 29 studies (>601 GPs, nurses and GP trainees) reporting views on discussing weight with patients. Key second-order themes were lack of confidence in treatments and patients' ability to make changes, interactional difficulty of discussing the topic, and a reluctance to accept responsibility to deal with patients with overweight and obesity. The third-order analytical theme was that discussions about weight were not a priority and other behavioural interventions, including smoking, often took precedent. GPs and nurses reported that noting BMI measurements at every consultation alongside a framework to deliver interventions would likely increased the frequency and perceived efficacy of behavioural weight interventions.

Interpretation: GPs and nurses acknowledge the importance of obesity as a health issue but this is insufficient, particularly amongst GPs, for them to construe this as a problem to address with patients in consultations. Strategies to implement clinical guidelines need to change this reluctance. Training to overcome interactional difficulties, regular weighing of patients, and changing expectations and understanding of weight loss interventions are the most promising of these strategies

O12

GDm-Health Plus: Development of a remote behavioural lifestyle management system for women with gestational diabetes

Pamela Dyson, Jane Hirst, Katy Bartlett, Yvonne Kenworthy, Angela Hargreaves, Sophie Roberts, Leticia Bradbury, Carmelo Velardo, Susan Jebb, Lionel Tarassenko, Lucy Mackillop

Aim: Preventing hyperglycaemia and excessive gestational weight gain through diet and physical activity are central to the management of women with gestational diabetes mellitus (GDM), although lifestyle change can be challenging. A remote digital blood glucose management system for women with GDM (GDm-health) has been evaluated previously, and the aim of this project was to test the feasibility of using this platform to support behavioural lifestyle change.

Methods: Women already using GDm-health, were offered voluntary participation in a service development project using a lifestyle app (GDm-health Plus). Women were asked to perform glucose monitoring, weekly self-weighing, carbohydrate counting and physical activity monitoring. Real time feedback was given by specialist dietitians and midwives. Quantitative evaluation assessed system usage, and qualitative analysis used a validated questionnaire (OMDTSQ).

Results: 18 women took part. Mean (SD) age 33.4(5.0) years, weight 92.4(27.1) kg. GDm-health Plus was introduced at mean 31.4(4.8) weeks gestation, with mean usage of 7.3 weeks. 11/18(61%) tested blood glucose at least 12 times weekly, 15/18(83%) recorded at least one weight but only 7/18(39%) recorded weight more than once, 14/18(78%) began carbohydrate counting and 16/18(89%) recorded physical activity. 13/18(72%) completed the satisfaction questionnaire and scores ranged from 3.7/4 (testing blood glucose) to 2.2/4 (feedback about weight).

Conclusion: In this small cohort of women with GDM, interaction with an enhanced app to monitor key behaviours was high, with the exception of self-weighing. Further evaluation of the efficacy of enhanced diet and physical activity support using digital health to address weight management is warranted.

O13
The experience of a research nurse working in obesity/metabolic disease

Jane Cheeseman

I am a research nurse and have been taking fat biopsies independently since 2005 and teaching the procedure to researchers all over the world since 2008 (Oxford, Johannesburg, Trondheim, Prague). Recently, I went to the MRC-funded facility in the Gambia to help a team starting a study on Type 2 diabetes in local women.

The unit in Gambia has been funded by the MRC since 1927 so I thought it would be like be just like our research facility here in Oxford. As you can see from my poster, it was a completely different story.

The room we used for the biopsies was set up for endoscopy procedures. There was a tall trolley with a few syringes already drawn up with some fluid but they were all unlabelled. The floor was very old lino. The nursing trolleys were probably from the 1950s, and when I put those syringes in the sharps bin ants came out. However, we soon had the room cleaned up, procedures in place and we were ready to start.

The team members were all very excited about starting the study, and were happy and willing to learn the new techniques needed to run the study to a high standard. Over the week, I taught them to confidently take and process the biopsies. The researcher has since come to Oxford to process, and analyse all the samples he collected and based on the support provided by us he has now submitted an application for a Wellcome Trust Clinical Training Fellowship.

Estimating the potential impacts of the Public Health England Sugar Reduction Strategy on child and adult health: a modelling study

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Objectives: Public Health England's Sugar Reduction Strategy includes working with industry to reduce the sugar content of certain foods as a way of reducing childhood obesity, but the potential health benefits have not been estimated. We modelled the possible impacts on child and adult obesity, adult disease burden and healthcare costs.

Design and Setting: The National Diet and Nutrition Survey waves 5 and 6 were used to simulate a scenario with the Sugar Reduction Strategy in place in England. Changes to child and adult weight were estimated, then the impacts of adult weight change on disease burden, healthcare costs were modelled using the PRIMEtime Model.

Participants: A total of 1,508 survey respondents were used to model the population of England aged 4-80 years.

Main outcome measures: Calorie change, weight change and BMI change were estimated for children and adults. Impact on non-communicable disease incidence, the associated Quality-Adjusted Life-Year impacts and healthcare costs were estimated for adults.

Results: If the Sugar Reduction Strategy were achieved in its entirety and resulted in the planned calorie reduction, then sugar reduction was estimated to be 25kcal/day for 4-10 year olds (95% Confidence Intervals 23-26kcal/day), 25kcal/day (24-28kcal/day) for 11-18 year-olds and 19kcal/day (17-20kcal/day) for adults. Body Mass Index was estimated to fall by $0.18kg/m^2$ (0.17-$0.19kg/m^2$) for 4-10 year-olds, $0.10kg/m^2$ (0.10-$0.11kg/m^2$) for 11-18 year-olds and $0.59kg/m^2$ (0.56-$0.62kg/m^2$) for 19-80 year-olds. A modelled 31,000 (95% Uncertainty Intervals 22,000-33,000) Quality-Adjusted Life-Years were saved over 10 years, including 114,000 (80,000-123,000) cases of diabetes and relating to a net healthcare saving of £180m (£125m-191m).

Conclusions: The Strategy could make a modest impact on obesity and obesity-related disease, provided that reductions in sugar levels and portion sizes do not prompt unanticipated changes in eating patterns or product formulation.

O15
PRIMORDIAL Study: Pregnancy Interventions In Mothers Relating to Diabetes In Asian India and Low-income countries

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Background: Excessive weight gain during pregnancy is associated with increased risk of gestational diabetes mellitus (GDM), caesarean deliveries, preeclampsia and postpartum weight retention, large-for-gestational-age infants, macrosomia, and childhood overweight or obesity. Lifestyle interventions during pregnancy are proven to have beneficial effects on gestational weight gain (GWG), development of GDM and improved neonatal outcomes. We aim to evaluate the effect of life-style interventions on GDM risk (mediated via GWG) in pregnant mothers from two ethnically diverse populations.

Study design: Pregnant women (n= 1,875, aged ≥ 18 years and between 12-16 weeks of gestational age) from India and The Gambia will be recruited in a 2x2 factorial randomized controlled trial. Randomization arms include either dietary intervention or physical activity (PA) intervention or diet + PA intervention or standard care for 16 weeks. The interventions include consumption of fermented yoghurt (200g/day) in the dietary arm and daily walking to targeted step count (40% increase from baseline) and participation in once weekly group training sessions (PA arm). The primary endpoint is GDM development assessed at 26-28 weeks or at 32 weeks. Secondary outcomes include continuous measures of fasting glucose at 26-28 weeks and 32 weeks, GWG, development of pre-eclampsia, intra-partum complications and new born weight.

Conclusion The current study will sensitise and expose pregnant women to specific healthy lifestyles. Behavioural changes during pregnancy targeted towards changing maternal nutrition and increasing PA can have immediate and lifelong beneficial health impact on the mother as well as the new born with possible positive consequences into adulthood.

The trial is funded by the MRC.

O16
The diabetes risk gene TCF7L2 regulates human adipose progenitor biology.

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Background and aims: Dysfunctional adipose tissue as seen in obesity or lipodystrophy is associated with insulin resistance (IR) which predisposes to type 2 diabetes (T2D) and cardiovascular disease (CVD). Nonetheless, the risk of T2D and CVD is not uniform in similarly obese subjects. The adipose tissue (AT) response to chronic caloric overload (hypertrophy *vs.* hyperplasia) is a major determinant of susceptibility to IR. TCF7L2 is a key transcription factor involved in WNT signalling, a developmental pathway, which has a central role in AT biology. A common SNP in TCF7L2 (rs7903146) is the strongest genetic determinant of T2D risk in humans. We hypothesised that TCF7L2 modulates T2D risk partly *via* effects on AT biology.

Materials and methods: *In vitro* functional studies in primary and immortalised human adipose progenitor cells (APCs) and AT phenotyping in rs7903146 risk variant carriers.

Results: *Ex vivo TCF7L2* expression was higher in APCs *versus* mature adipocytes (mADs) ($p<0.001$, n=108-114) and adipose endothelial cells ($p<0.01$, n=5-6) in both subcutaneous abdominal and gluteal depots. *TCF7L2* expression correlated positively with BMI *selectively* in abdominal APCs ($p=0.006$, R=0.27, n=107). Stable TCF7L2 knockdown (KD) with two independent shRNAs (low and high efficiency) targeting the same exon led to impaired cell proliferation ($p<0.01$) and a dose-dependent increase in WNT signalling ($p<0.001$) in immortalised human abdominal APCs. Notably, adipogenesis was enhanced ($p<0.001$) with low efficiency TCF7L2 KD whilst being impaired ($p<0.001$) with high efficiency TCF7L2 KD in both immortalised and primary human abdominal APCs. Compared with homozygous non-risk allele (C) carriers, homozygous carries of the T2D risk allele (T) at rs7903146 displayed reduced *ex vivo* TCF7L2 mRNA ($p=0.016$, n=19-54) and protein ($p=0.02$, n=11) levels in abdominal APCs. Accordingly, and consistent with chromatin state data from human APCs showing that rs7903146 overlaps a weak enhancer, *in vitro* reporter assays revealed that the T2D risk allele (T) abrogates enhancer activity in abdominal APCs (C *vs.* T, $p<0.001$). Lastly, compared with homozygous carriers of the C allele, individuals homozygous for the T2D risk allele (T) displayed altered adipocyte size distribution in abdominal AT ($p<0.01$, n=19).

Conclusion: These results implicate TCF7L2 in human adipose progenitor biology and AT plasticity and suggest that rs7903146 modulates susceptibility to T2D partly *via* effects on APCs.

Disclosure: This work was supported by Oxford-Novo Nordisk Postdoctoral

O17

The effect of weight-loss interventions on non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomised controlled trials

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Introduction: Non-alcoholic fatty liver disease (NAFLD) affects about 25% of adults worldwide and is strongly linked with obesity. Weight loss may improve liver function in people with NAFLD, but its effects have not been previously quantified. We aimed to examine if weight loss interventions in people with NAFLD affect liver function.

Methods: We searched 9 databases (March 2018) for randomised controlled trials in people with NAFLD of any intervention aiming to reduce weight, including behavioural weight loss programmes (BWLPs), pharmacotherapy, and surgery that recorded any index of liver disease as an outcome (PROSPERO ID: CRD42018088882). Two independent reviewers screened the studies and extracted the data, and assessed the risk of bias using the Cochrane tool. Random effect meta-analyses were conducted.

Results: Twenty-one studies met the inclusion criteria (24 comparisons, 2420 participants), of which 13 tested BWLPs, 7 pharmacotherapy with or without a BWLP, and 1 surgery with a BWLP. The median intervention duration was 6 months (IQR: 6 months) and all trials examined outcomes at intervention completion. Compared with minimal or less intensive interventions, participants in the more intensive weight loss interventions lost significantly more weight (-3.6kg, 95% CI: -5.2, -1.9, n=22 comparisons) and significantly improved fasting glucose and HbA1c. Blood markers for liver disease significantly improved including ALT (-8.2U/L, 95% CI: -11.7, -4.7, n=23 comparisons) and AST (-4.5U/L, 95% CI: -7.0, -2.0, n=22 comparisons). Weight loss reduced liver steatosis measured by histology, MRI, or ultrasound (SMD: -1.5, 95% CI: -2.3, -0.7, n=12 comparisons), NAS activity score (-0.9, 95% CI: -1.8, -0.1, n=6 comparisons), and presence of definite NASH (OR: 0.1, 95% CI: 0.04, 0.5, n=2 comparisons). There was no significant change in liver fibrosis score (-0.1, 95% CI: -0.5, 0.3, n=6 comparisons). Most estimates did not materially change when studies with high risk of bias (n=10) were excluded.

Conclusion: Weight loss leads to statistically and clinically significant improvements in liver function in people with NAFLD in the short-term. Trials with longer-term follow-up are needed.

Conflict of interest: None declared.

O18
Tackling Statin Intolerance with N-of-1 trials in primary care (TaSINI): testing the feasibility of a GP delivered behavioural intervention to increase statin adherence.

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Background: Systematic reviews of randomised trials show that statins reduce the incidence of cardiovascular disease. However, about half of all patients prescribed statins in normal clinical practice discontinue use in the first year, often due to fear of or perceived side-effects. A meta-analysis of randomised controlled trials found many of the adverse effects commonly attributed to statins were no more common in the statin arm than the placebo arm; indicating that many people classified as statin intolerant may, in fact, be tolerant of them but persuading people to distrust their own experience is difficult. One approach may be to enrol people who fear or have experienced 'side-effects' into an n-of-1 trial where participants alternate between medication and no medication/placebo. A recent n-of-1 trial enrolled people with statin intolerance and, once participants discovered their 'side-effects' occurred as commonly when taking placebo as statin, they resumed regular medication. However, blinded trials are impossible in routine care so the aim of this trial is to show whether a GP-delivered behavioural intervention incorporating open-label n-of-1 trials can increase adherence to statin medication in people who have declined or stopped statin due to intolerance.

Methods: 90 adult patients with a cardiovascular risk score indicating statin therapy is appropriate in general practice surgeries will be randomised, 1:1:1 to intervention (open-label n-of-1), positive control (closed-label i.e. placebo-controlled n-of-1), or control (usual care). The intervention will be delivered by GPs who will provide patients with evidence-based information about statins, explanation of the n-of-1 approach, and reinforce this with a booklet. Participants in both n-of-1 groups will alternate between four-week 'on' and 'off' periods of taking statins for a total of 24 weeks. Participants in both n-of-1 groups will be asked to record their symptoms and whether they attribute them to the statin in the last week of each four-week period. At a six-month follow up visit the GP will feedback participants' symptoms and attribution scores while they were 'on' and 'off' the statin. The GP will discuss and record whether patients decide to continue taking statin medication.

Conclusions: We will assess whether a full trial with LDL concentration is feasible by examining the proportions of people invited that participate, the proportion that accept the GP's invitation to undertake an n-of-1 trial, and the proportion that continue statins at six months.

O19

A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss

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Meal replacements (MR) are generally not recommended in clinical guidelines for the management of obesity. The aim of this review is to provide an up-to-date systematic evaluation of the effect of weight loss interventions incorporating MR compared with alternative interventions on weight change at 1 year in adults with overweight or obesity. Six electronic databases were searched from inception to the end of August 2018 for randomized controlled trials comparing the effect of MR with interventions that did not include MR on weight at 1 year. We excluded studies using diets providing <3347 kJ/(800 kcal)/day and those which used total diet replacement (TDR) from this review. Risk of bias was assessed using the Cochrane risk of bias tool. Twenty-three studies with 7884 adult participants were included. Six out of 23 studies were judged at low risk of bias across all domains, and 5/23 studies were judged at high risk of bias in at least one domain. Studies with similar intervention and comparators were grouped into five comparisons for analysis. Mean weight change at 1 year favoured the MR group relative to the control group in each comparison. In those comparisons where we conducted meta-analysis, in people assigned to a diet incorporating MR, mean difference was -1.44 kg (-2.48 to -0.39 kg; $I^2 = 38\%$) compared with alternative kinds of diets. In those assigned to a MR diet along with support, mean difference was -2.22 kg (-3.99 to -0.45, $I^2 = 81\%$) compared with other diets with support and -3.87 kg (-7.34 to -0.40; $I^2 = 60\%$) compared with other kinds of diet without support. In those assigned a MR diet with an enhanced level of support, mean difference was -6.13 kg (-7.35 to -4.91, $I^2 = 19\%$) compared with alternative diets and regular support. Programmes incorporating meal replacements led to greater weight loss at 1 year than comparator weight loss programmes and should be considered as a valid option for management of overweight and obesity in community and health care settings.

S1

Does surgery for asymptomatic carotid stenosis reduce the long-term risk of dementia and stroke? Extended post-trial follow-up of the Asymptomatic Carotid Surgery Trial (ACST-1)

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Background and Objectives:
Patients with significant narrowing of the carotid arteries ('carotid stenosis') are at higher risk of stroke when particles from the narrowing break off and block blood supply to part of the brain. Some studies suggest this may also lead to a higher risk of dementia.

Stroke risk can be halved by an operation to remove carotid stenosis ('carotid endarterectomy'), but it is unclear whether the operation also reduces dementia risk.

We are investigating whether an operation reduces dementia risk with long-term follow-up of 1601 ACST-1 participants (1069 UK: 532 Sweden), with carotid stenosis, but no stroke, who were randomly allocated carotid endarterectomy or no operation.

Methods/processes:
Dementia identified from the first record found in:
  i)   Blinded review of paper ACST-1 files up to 2008
  ii) Data linkage with hospital and mortality electronic health records up to 2018 (datasets received from NHS Digital for England, equivalent bodies in Scotland & N. Ireland, Swedish Socialstyrelsen and Swedish Dementia Registry)
  iii) Use of Short IQCODE questionnaire for current cognition in survivors

Dementia diagnosis identified from ICD 10 coding in linked datasets and grouped as Alzheimer's, vascular dementia, unspecified, rare or other. Data for any stroke and cause of death was also collected.

Results/evaluation:
Data linkage and paper file review is complete and analyses ongoing. Quality of the match of the ACST-1 linked data with electronic health records ranked as 1 and 2 therefore the information we supplied enabled close matching with the information in each dataset ('match ranking system' provided by NHS Digital where the quality of the match is denoted by the rank i.e.1 being the highest quality match). Of 1601 participants, on joining ACST-1, 441 (27.5%) were <65 years of age, 784 (49%) were 65-74 years and 376 (23.4%) were 75 years or older.

Conclusion/perspectives:
This is the first study to determine long-term cognitive decline and dementia risk in patients with severe carotid disease. The study demonstrates that long-term linkage of randomised trials with electronic health records is possible.

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S2
Large artery atheromatous disease and cerebral small vessel disease: a post mortem study

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Introduction

Vascular risk factors are associated with both systemic and cerebral vascular disease. However, the relationship between large artery atheromatous disease and cerebral small vessel disease (SVD) is not completely understood. Carotid atheroma has been reported to have a small effect on brain white matter (WM) changes, an indirect marker of SVD. However these WM changes could be due to chronic hypoperfusion related to the large vessel stenosis and not to structural changes in the cerebral small vessels. A stronger association between cervical, intracranial and aortic arterial atheroma and other SVD imaging markers has been reported but these observations have not been confirmed histologically.

Aim

The aim of this study is to investigate the relationship between large artery atheromatous disease and histologically confirmed SVD.

Methods

A semi-quantitative score (6) was applied to assess the extent of atheroma in the aorta, coronary, cervical (carotid and vertebral) and intracranial arteries, from autopsy reports of a human post-mortem cohort (19722005). Mean aorta and coronary atheroma scores were combined to generate a systemic atheroma index (SAO. H&E sections from formalin-fixed paraffin-embedded tissue from frontal WM (FWM) (a), occipital WM (OWM) (b), basal ganglia (BG), (c) and pons (d) (Figure 2) were used to assess the extent of SVD using recently published criteria. SVD ratings were obtained by one rater (RG) and confirmed by second rater (ME) in a subset of cases. The 2 raters were blinded for the large artery atheroma scores and a total SVA score was calculated.

Results

A total of 39 subjects were included, mean age 58.8±12.9 years, 56.4% females, 28.2% died of vascular disease, 28.2% of cancer, 12.8% of infection. Cervical artery (r=0.40, p=0.038) and intracranial artery (r=0.48, p=0.008) disease significantly increased with age at death, but this relationship was not seen with SAI (r=0.22, p=0.164). Total SVD score did not differ between men and women and increased with age at death (r=0.387 p= 0.015). No correlation was found between total SVD and heart weight (r=0.15, p=0.35) Total SVD score increased

with cervical atheroma severity (r=0.37, p=0.02), with intracranial artery atheroma (r=0.359, p=0.051) but no significant correlation was found with SAI (r=0.165, p=0.34).

Conclusion

Our preliminary data supports a relationship between cervical atheroma and SVD. A similar relationship between aorta + coronary artery atheromatous disease and SVD was not found. Future studies evaluating SVD should consider the impact of cervical artery atheroma.

S3
Diurnal variation in performance on telephone cognitive screening in older subjects

Aubretia McColl

Abstract not available for distribution.

S4
Influence of age on prognosis of cryptogenic stroke with PFO on medical treatment alone: systematic review and meta-regression

Sara Mazzucco

Abstract not available for distribution.

S5
Does season affect telephone cognitive screening performance in older subjects?

Aubretia McColl

Abstract not available for distribution.

S6
Increased long-term risk of intracerebral haemorrhage after transient neurological attacks: a population based study

Maria A. Tuna

Abstract not available for distribution.

S7
The Role of the TSC1-TSC2 Complex in Selective Neuronal Degeneration in Alzheimer's Disease.

Bryan A. Adriaanse, Sinead Brady, Adele Smart, Abishek Arora, Gabriele C. De Luca, M. Zameel Cader

Abstract not available for distribution.

S8
Cerebral small vessel disease in multiple sclerosis .

Ruth Geraldes, Margaret Esiri, Jacqueline Palace, Gabriele C. DeLuca

Abstract not available for distribution.