NHS Research Scotland (NRS) Primary Care

Publications Newsletter No. 4, January 2025

Dear colleagues

Welcome to the fourth issue of our Publications Newsletter.

Below you will find recent publications from studies that the Network and GP practices across Scotland have supported. We hope this will help the practice to keep up to date with the literature, and that GPs find it useful for their appraisal. The papers are presented in order of project name.

Best wishes

https://www.nhsresearchscotland.org.uk/research-areas/primary-care

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Project: **ADxDA**

Title of paper: Use and acceptability of an asthma diagnosis clinical decision support system for primary care clinicians: an observational mixed methods study

Reference: NPJ Prim. Care Respir. Med. 34, 40 (2024)

Authors: Daines *et al.*

url: https://doi.org/10.1038/s41533-024-00401-x

Summary: There is uncertainty about how best to diagnose asthma, especially in primary care where mis-diagnosis is common. To address this, we developed a clinical decision support system (CDSS) for asthma diagnosis in children and young people (aged 5-25 years). This study explored the feasibility and acceptability of the CDSS in UK primary care. We recruited general practices from England and Scotland. The CDSS was available for use during routine consultations for six months. We analysed CDSS usage and, toward the end of the study, undertook qualitative interviews with clinicians who had used the CDSS. Within the 10 practices who completed the study, the CDSS was used by 75 out of 94 clinicians. 11 clinicians from 8 practices were interviewed. The CDSS was acceptable to participants who particularly commented on the ease of use and auto-population of information from the patient record. Barriers to use included the inability to record findings directly into the patient notes and a sense that, whilst possibly useful for trainees and junior colleagues, the CDSS would not necessarily lead to a change in their own practice. The CDSS was generally well received by primary care clinicians, though participants felt it would be most useful for trainees and less experienced colleagues.

Project **ALL-HEART**

Title of paper: Allopurinol and cardiovascular outcomes in patients with ischaemic heart disease: the ALL-HEART RCT and economic evaluation

Reference: Health Technology Assessment Volume: 28, Issue: 18 March 2024

Authors: Mackenzie et al

url: https://doi.org/10.3310/

Summary: **Background**: Allopurinol is a xanthine oxidase inhibitor that lowers serum uric acid and is used to prevent acute gout flares in patients with gout. Observational and small interventional studies have suggested beneficial cardiovascular effects of allopurinol.

Objective: To determine whether allopurinol improves major cardiovascular outcomes in patients with ischaemic heart disease.

Design: Prospective, randomised, open-label, blinded endpoint multicentre clinical trial.

Setting: Four hundred and twenty-four UK primary care practices.

Participants: Aged 60 years and over with ischaemic heart disease but no gout.

Interventions: Participants were randomised (1 : 1) using a central web-based randomisation system to receive allopurinol up to 600 mg daily that was added to usual care or to continue usual care.

Main outcome measures: The primary outcome was the composite of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death. Secondary outcomes were non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, all-cause mortality, hospitalisation for heart failure, hospitalisation for acute coronary syndrome, coronary revascularisation, hospitalisation for acute coronary syndrome or coronary revascularisation, all cardiovascular hospitalisations, quality of life and cost-effectiveness. The hazard ratio (allopurinol vs. usual care) in a Cox proportional hazards model was assessed for superiority in a modified intention-to-treat analysis.

Results: From 7 February 2014 to 2 October 2017, 5937 participants were enrolled and randomised to the allopurinol arm (n = 2979) or the usual care arm (n = 2958). A total of 5721 randomised participants (2853 allopurinol; 2868 usual care) were included in the modified intention-to-treat analysis population (mean age 72.0 years; 75.5% male). There was no difference between the allopurinol and usual care arms in the primary endpoint, 314 (11.0%) participants in the allopurinol arm (2.47 events per 100 patient-years) and 325 (11.3%) in the usual care arm (2.37 events per 100 patient-years), hazard ratio 1.04 (95% confidence interval 0.89 to 1.21); p = 0.65. Two hundred and eighty-eight (10.1%) participants in the allopurinol arm and 303 (10.6%) participants in the usual care arm died, hazard ratio 1.02 (95% confidence interval 0.87 to 1.20); p = 0.77.

The pre-specified health economic analysis plan was to perform a ‘within trial’ cost-utility analysis if there was no statistically significant difference in the primary endpoint, so NHS costs and quality-adjusted life-years were estimated over a 5-year period. The difference in costs between treatment arms was +£115 higher for allopurinol (95% confidence interval £17 to £210) with no difference in quality-adjusted life-years (95% confidence interval −0.061 to +0.060). We conclude that there is no evidence that allopurinol used in line with the study protocol is cost-effective.

Project: **AnTIC**

Title of paper: Efficacy of antibiotic prophylaxis among intermittent catheter users with different neurologic diseases: A secondary analysis of the AnTIC Trial

Reference: Continence Volume 1, March 2022, 100004

Authors: Welk et al

url: https://doi.org/10.1016/j.cont.2022.100004

Summary: **Objective:** To use existing clinical trial data to assess the impact of prophylactic antibiotics on the 1-year UTI rate among people with different neurologic diseases, and to determine if

UTIs impact renal function.

Methods: We conducted a secondary analysis of community dwelling participants with a neurologic disease and intermittent catheter use who participated in a 12-month randomized trial (AnTIC) of low dose antibiotic prophylaxis. We calculated incident rate ratios (IRR) of symptomatic UTIs that required antibiotics. Renal function was assessed using the estimated glomerular filtration rate.

Results: We identified 138 patients who had a neurologic disease (multiple sclerosis (25%), spinal cord injury (21%), spina bifida (18%), and other disorders (36%)). The incidence of symptomatic, antibiotic treated urinary infections was 1.48 per person–year in the prophylaxis group, and 2.51 per person–year in the usual care group; the IRR was 0.59 (95% CI 0.46, 0.76) in favor of continuous antibiotic prophylaxis. The IRR was lowest (most protective) among those with spinal cord injury (IRR 0.23, $p < 0.01$) and highest (least protective) in those with spina bifida (IRR 0.85, $p = 0.57$). There were small, non-significant decreases in renal function that did not differ by randomization. There were no significant differences in pre- and post-study renal function based on the number of UTIs participants experienced.

Conclusion: Continuous antibiotic prophylaxis may be more effective for certain patient populations with neurologic lower urinary tract dysfunction. Renal function is not significantly impacted by a higher number of UTIs over the course of one year.

(**Previous publication** – Continuous low-dose antibiotic prophylaxis for adults with repeated urinary tract infections (AnTIC): a randomised, open-label trial by Fisher et al in The Lancet Infectious Diseases, 18:9 2018, pp 957-68 https://doi.org/10.1016/S1473-3099(18)30279-2)

Project: **ARRISA-2**

Title of paper: At-risk registers integrated into primary care to stop asthma crises in the UK (ARRISA)

Reference: Thorax 2024;79:A76

Authors: Wilson et al

url: https://thorax.bmj.com/content/79/Suppl_2/A76.1

Summary: **Background**: Avoiding emergency hospital admissions is a crucial aspect of asthma care. A small-scale regional trial suggested that the implementation of at-risk registers for asthma in primary care may improve hospital admission rates.

Aim: To assess, via a national study, whether the ARRISA-UK intervention reduced asthma crisis events.

Methods: Cluster randomised trial of a complex intervention across 275 UK primary care practices. The intervention comprised of identification of those at-risk, practice-based training regarding at-risk asthma, a clinical decision support system alerting practice staff to patients' at-risk status to facilitate prompt and opportunistic care, and practice support. Control practices continued with usual care. Patients (n=10945) were included if they were identified as being at-risk unless they declined data sharing. Routine data, with linkage between primary and secondary care, captured the primary endpoint of asthma-related crisis events (hospitalisation, A&E attendances or death). The number of prescriptions of prednisolone for asthma attacks was captured amongst other processes of care.

Results: Data from 185 practices (6207 patients) were available for a complete case analysis. There was no significant effect on the asthma crisis events: intervention 185/2959 (6.3%) control 235/3248 (7.2%) odds ratio (OR) 0.87 (95% CI 0.69,1.09; p=0.220), nor for the components of this composite endpoint. When adjusting for any baseline asthma-related hospitalisation and A&E attendance the adjusted OR was 0.82 (0.66,1.03; p=0.088).

There was no significant difference in prescriptions of prednisolone: intervention 1116, control 1234 OR 1.2(0.99,1.5; p=0.062) nor when adjusted OR 1.17 (0.98, 1.4; p=0.074).

Conclusion: The primary analysis did not show a statistically significant effect of the ARRISA intervention on the primary outcome. Further analysis is required to determine whether this intervention is cost-effective and to identify subgroups that may have benefitted.

Project: **BiCARB** - Bicarbonate for Chronic Kidney Disease and Acidosis

Title of paper: Oral Sodium Bicarbonate Therapy for Older Patients with Chronic Kidney Disease and Low-Grade Acidosis: The BiCARB Randomised Controlled Trial

Reference: Age and Ageing, Volume 49, Issue Supplement_1, February 2020, Pages i34–i3

Authors: Witham et al

url: https://doi.org/10.1093/ageing/afz196.06

Summary: **Background**: Oral sodium bicarbonate is often used to treat metabolic acidosis in older people with advanced chronic kidney disease, but evidence is lacking on whether this provides a net gain in health or quality of life.

Methods: We conducted a multicentre, parallel group, double-blind, placebo-controlled randomised trial. Adults aged 60 years and over with category 4 or 5 chronic kidney disease, not on dialysis, with serum bicarbonate concentrations <22 mmol/L were recruited from 27 UK centres. Participants were randomised 1:1 to oral sodium bicarbonate or matching placebo. The primary outcome was the between-group difference in the Short Physical Performance Battery at 12 months, adjusted for baseline. Other key outcome measures included generic and disease-specific health-related quality of life, anthropometry, physical performance, renal function, adverse events including commencement of renal replacement therapy, and health economic analysis.

Results: We randomised 300 participants, mean age 74 years; 86 (29%) were female. Mean baseline estimated GFR was 19 ml/min/1.73m2. Study medication adherence was 73% in both groups. No significant treatment effect was evident for the primary outcome of the between-group difference in the Short Physical Performance Battery at 12 months (-0.4 points; 95% CI -0.9 to 0.1, p=0.15). No significant treatment benefit was seen for any of the secondary outcomes. Adverse events were more frequent in the bicarbonate arm (457 versus 400). Time to commencing renal replacement therapy was similar in both groups (HR 1.22, 95% CI 0.74 to 2.02, p=0.43). Health economic analysis showed lower quality of life and higher costs in the bicarbonate arm at one year (£1234 vs £807); placebo dominated bicarbonate under all sensitivity analyses for incremental cost-effectiveness.

Conclusions: Oral sodium bicarbonate did not improve a wide range of health measures in this trial, and is unlikely to be cost-effective for use in the UK NHS in this patient group.

Project: **BICS**

Title of paper: Bisoprolol in Patients With Chronic Obstructive Pulmonary Disease at High Risk of Exacerbation The BICS Randomized Clinical Trial

Reference: JAMA. 2024;332(6):462-470

Authors: Devereux et al

url: doi:10.1001/jama.2024.8771

Summary: **Importance:** Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Observational studies report that β-blocker use may be

associated with reduced risk of COPD exacerbations. However, a recent trial reported that metoprolol did not reduce COPD exacerbations and increased COPD exacerbations requiring hospital admission.

Objective: To test whether bisoprolol decreased COPD exacerbations in people with COPD at high risk of exacerbations.

Design, **Setting**, **and Participants:** The Bisoprolol in COPD Study (BICS) was a double-blind placebo-controlled randomized clinical trial conducted in 76 UK sites (45 primary care clinics and 31 secondary clinics). Patients with COPD who had at least moderate airflow obstruction on spirometry (ratio of forced expiratory volume in the first second of expiration [FEV1] to forced vital capacity <0.7; FEV1 <80% predicted) and at least 2 COPD exacerbations treated with oral corticosteroids, antibiotics, or both in the prior 12 months were enrolled from October 17, 2018, to May 31, 2022. Follow-up concluded on April 18, 2023.

Interventions: Patients were randomly assigned to bisoprolol (n = 261) or placebo (n = 258). Bisoprolol was started at 1.25 mg orally daily and was titrated as tolerated during 4 sessions to a maximum dose of 5 mg/d, using a standardized protocol.

Main outcomes and measures: The primary clinical outcome was the number of patient-reported COPD exacerbations treated with oral corticosteroids, antibiotics, or both during the 1-year treatment period. Safety outcomes included serious adverse events and adverse reactions.

Results: Although the trial planned to enroll 1574 patients, recruitment was suspended from March 16, 2020, to July 31, 2021, due to the COVID-19 pandemic. Two patients in each group were excluded post-randomization. Among the 515 patients (mean [SD] age, 68 [7.9] years; 274 men [53%]; mean FEV1, 50.1%), primary outcome data were available for 514 patients (99.8%) and 371 (72.0%) continued taking the study drug. The primary outcome of patient-reported COPD exacerbations treated with oral corticosteroids, antibiotics, or both was 526 in the bisoprolol group, with a mean exacerbation rate of 2.03/y, vs 513 exacerbations in the placebo group, with a mean exacerbation rate of 2.01/y. The adjusted incidence rate ratio was 0.97 (95% CI, 0.84-1.13; P = .72). Serious adverse events occurred in 37 of 255 patients in the bisoprolol group (14.5%) vs 36 of 251 in the placebo group (14.3%; relative risk, 1.01; 95% CI, 0.62-1.66; P = .96).

Conclusions and Relevance: Among people with COPD at high risk of exacerbation, treatment with bisoprolol did not reduce the number of self-reported COPD exacerbations requiring treatment with oral corticosteroids, antibiotics, or both.

Project: **Cancer and Comorbidity Study**

Title of paper: Living With and Beyond Cancer With Comorbid Conditions: Qualitative Insights to Understand Psychosocial Support Needs

Reference: Health Expectations, 27: e70039 (October 2024)

Authors: Cavers et al

url: https://doi.org/10.1111/hex.70039

Summary: **Introduction:** There is a pressing need to understand and explore the complex experiences and psychosocial support needs of people LWBC-CM and their informal caregivers, to inform survivorship and supportive care interventions.

Methods: In-depth qualitative interviews were conducted with people LWBC-CM and their informal caregivers in Scotland, invited via primary care. One-to-one, face-to-face interviews were conducted with informed consent exploring experiences of symptoms, psychosocial support needs and interactions with health services. Interviews were transcribed and

analysed using a thematic approach.

Results: Forty-one people LWBC-CM and twenty-three informal caregivers were interviewed. Four themes were identified: the Physical and Psychological Impact of Cancer and Comorbidity, Dominant Storie—Prioritising Conditions and Making Sense of Illness, Navigating Health Services and Treatments and Caring for People with Complex Health Conditions. Type and severity of conditions mediated people's experiences and daily living. Complex fatigue—fatigue arising from a number of health conditions—dominated symptomology. Participants navigated multiple appointments and complex medication regimes. Patients identified the need for acknowledgement of other chronic conditions and for streamlined care provision. Mutual caring and social isolation were also identified as part of the caring relationship.

Conclusions: There is a mandate to address the psychosocial support needs of people LWBC-CM, and their informal carers, given the burden of treatment for cancer survivors with moderate to severe complex conditions as they navigate health services.

Project: **CATHETER II**

Title of paper: CATHETER II: a randomised controlled trial comparing the clinical effectiveness of various washout policies versus no washout policy in preventing catheter-associated complications in adults living with long-term catheters

Reference: BMJ Open. 2024 Dec 2;14(12):e087203

Authors: Abdel-Fattah et al

url: doi: 10.1136/bmjopen-2024-087203

Summary: **Objectives:** Do weekly prophylactic saline or acidic catheter washouts in addition to standard long-term catheter (LTC) care improve the outcomes of adults with LTC compared with standard LTC care only.

Design, setting and participants: Three-arm superiority open-label randomised controlled trial; UK community-based study; 80 adults with LTC (any type/route) ≥28 days in situ with no plans to discontinue and able to self-manage the washouts/study documentation with/without a carer.

Interventions: Randomly allocated (26:27:27) to receive standard LTC care with weekly saline or weekly acidic or no prophylactic washouts for up to 24 months.

Primary and secondary outcome measures: The primary outcome was catheter blockage requiring intervention (per 1000 catheter days). Secondary outcomes were symptomatic catheter-associated urinary tract infection (S-CAUTI) requiring antibiotics, adverse events, participants' quality of life and day-to-day activities, acceptability and adherence.

Results: Outcomes reported for 25 saline, 27 acidic and 26 control participants. LTC blockages (per 1000 catheter days) requiring treatment were 9.96, 10.53 and 20.92 in the saline, acidic and control groups, respectively. The incident rate ratio (IRR) favours the washout groups (saline 0.65 (97.5% CI 0.24 to 1.77); p=0.33 and acidic 0.59 (97.5% CI 0.22 to 1.63); p=0.25), although not statistically significant. The S-CAUTI rate (per 1000 catheter days) was 3.71, 6.72 and 8.05 in the saline, acidic and control groups, respectively. The IRR favours the saline group (saline 0.40 (97.5% CI 0.20 to 0.80); p=0.003 and acidic 0.98 (97.5% CI 0.54 to 1.78); p=0.93). The trial closed before reaching target recruitment due to reduced research capacity during the COVID-19 pandemic.

Conclusions: Early closure and small sample size limits our ability to provide a definite answer. However, the observed non-statistically significant differences over control are favourable for lower rates of LTC blockages without a concomitant rise in S-CAUTI. The results support a multinational randomised controlled trial of catheter washouts in patients

with LTC to ascertain their clinical and cost-effectiveness.

Project: **EVIDENCE**

Title of paper: Evaluating Diuretics in Normal Care (EVIDENCE) – a cluster randomised evaluation of prescribing policy for hypertension

Reference: Pilot and Feasibility Studies volume 8, Article number: 62 (2022)

Authors: Flynn et al

url: DOI: 10.1186/s40814-022-01016-0

Summary: **Background**: Obtaining evidence on comparative effectiveness and safety of widely prescribed drugs in a timely and cost-effective way is a major challenge for healthcare systems. Here, we describe the feasibility of the Evaluating Diuretics in Normal Care (EVIDENCE) study that compares a thiazide and thiazide-like diuretics for hypertension as an exemplar of a more general framework for efficient generation of such evidence. In 2011, the UK NICE hypertension guideline included a recommendation that thiazide-like diuretics (such as indapamide) be used in preference to thiazide diuretics (such as bendroflumethiazide) for hypertension. There is sparse evidence backing this recommendation, and bendroflumethiazide remains widely used in the UK.

Methods: Patients prescribed indapamide or bendroflumethiazide regularly for hypertension were identified in participating general practices. Allocation of a prescribing policy favouring one of these drugs was then randomly applied to the practice and, where required to comply with the policy, repeat prescriptions switched by pharmacy staff. Patients were informed of the potential switch by letter and given the opportunity to opt out. Practice adherence to the randomised policy was assessed by measuring the amount of policy drug prescribed as a proportion of total combined indapamide and bendroflumethiazide. Routinely collected hospitalisation and death data in the NHS will be used to compare cardiovascular event rates between the two policies.

Results: This pilot recruited 30 primary care practices in five Scottish National Health Service (NHS) Boards. Fifteen practices were randomised to indapamide (2682 patients) and 15 to bendroflumethiazide (3437 patients), a study population of 6119 patients. Prior to randomisation, bendroflumethiazide was prescribed to 78% of patients prescribed either of these drugs. Only 1.6% of patients opted out of the proposed medication switch.

Conclusion: The pilot and subsequent recruitment confirms the methodology is scalable within NHS Scotland for a fully powered larger study; currently, 102 GP practices (> 12,700 patients) are participating in this study. It has the potential to efficiently produce externally valid comparative effectiveness data with minimal disruption to practice staff or patients. Streamlining this pragmatic trial approach has demonstrated the feasibility of a random prescribing policy design framework that can be adapted to other therapeutic areas.

Project: **FLOW** Semaglutide renal outcomes trial

Title of paper: Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease

Reference: N Engl J Med 2024 Jul 11;391(2):109-121

Authors: Perkovic et al

url: DOI: 10.1056/NEJMoa2403347

Summary: (Novo Nordisk study)

Background: Patients with type 2 diabetes and chronic kidney disease are at high risk for

kidney failure, cardiovascular events, and death. Whether treatment with semaglutide would mitigate these risks is unknown.

Methods: We randomly assigned patients with type 2 diabetes and chronic kidney disease (defined by an estimated glomerular filtration rate [eGFR] of 50 to 75 ml per minute per 1.73 m2 of body-surface area and a urinary albumin-to-creatinine ratio [with albumin measured in milligrams and creatinine measured in grams] of >300 and <5000 or an eGFR of 25 to <50 ml per minute per 1.73 m2 and a urinary albumin-to-creatinine ratio of >100 and <5000) to receive subcutaneous semaglutide at a dose of 1.0 mg weekly or placebo. The primary outcome was major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes. Prespecified confirmatory secondary outcomes were tested hierarchically.

Results: Among the 3533 participants who underwent randomization (1767 in the semaglutide group and 1766 in the placebo group), median follow-up was 3.4 years, after early trial cessation was recommended at a prespecified interim analysis. The risk of a primary-outcome event was 24% lower in the semaglutide group than in the placebo group (331 vs. 410 first events; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.88; P = 0.0003). Results were similar for a composite of the kidney-specific components of the primary outcome (hazard ratio, 0.79; 95% CI, 0.66 to 0.94) and for death from cardiovascular causes (hazard ratio, 0.71; 95% CI, 0.56 to 0.89). The results for all confirmatory secondary outcomes favored semaglutide: the mean annual eGFR slope was less steep (indicating a slower decrease) by 1.16 ml per minute per 1.73 m2 in the semaglutide group (P<0.001), the risk of major cardiovascular events 18% lower (hazard ratio, 0.82; 95% CI, 0.68 to 0.98; P = 0.029), and the risk of death from any cause 20% lower (hazard ratio, 0.80; 95% CI, 0.67 to 0.95, P = 0.01). Serious adverse events were reported in a lower percentage of participants in the semaglutide group than in the placebo group (49.6% vs. 53.8%).

Conclusions: Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease.

Project: **iPREVENT**

Title of paper: Increase in colonic PRopionate as a method of prEVENTing weight gain over 12 months in adults aged 20-40 years (iPREVENT): a multi-centre, double-blind, randomised, parallel-group trial

Reference: EClinicalMedicine. 2024 Sep 25;76:102844

Authors: Pugh et al

url: DOI: 10.1016/j.eclinm.2024.102844

Summary: **Background**: Obesity drives metabolic disease development. Preventing weight gain during early adulthood could mitigate later-life chronic disease risk. Increased dietary fibre intake, leading to enhanced colonic microbial fermentation and short-chain fatty acid (SCFA) production, is associated with lower body weight. Despite national food policy recommendations to consume 30 g of dietary fibre daily, only 9% of adults achieve this target. Inulin-propionate ester (IPE) selectively increases the production of the SCFA propionate in the colon. In previous studies, IPE has prevented weight gain in middle-aged adults over 6 months, compared with the inulin control. IPE is a novel food ingredient that can be added to various commonly consumed foods with a potential health benefit. This 12-month study aimed to determine whether using IPE to increase colonic propionate prevents further weight gain in overweight younger adults.

Methods: This multi-centre randomised-controlled, double-blind trial was conducted in London and Glasgow, UK. Recruited participants were individuals at risk of weight gain, aged between 20 and 40 years and had an overweight body mass index. Sealed Envelope Software was used to randomise participants to consume 10 g of IPE or inulin (control), once per day for 12 months. The primary outcome was the weight gained from baseline to 12 months, analysed by an 'Intention to Treat' strategy. The safety profile and tolerability of IPE were monitored through adverse events and compliance. This study is registered with the International

Findings: Participants (n = 135 per study arm) were recruited from July 2019 to October 2021. At 12 months, there was no significant difference in baseline-adjusted mean weight gain for IPE compared with control (1.02 kg, 95% CI: -0.37 to 2.41; p = 0.15; n = 226). Neither the IPE (+1.22 kg) nor the control arm (+0.07 kg) unadjusted mean gains in body weight reached the expected 2 kg threshold. In the IPE arm, fat-free mass was greater by 1.07 kg (95% CI: 0.21-1.93), and blood glucose elevated by 0.11 mmol/L (95% CI: 0.01-0.21). Compliance, determined by intake of ≥50% sachets, was reached by 63% of IPE participants. There were no unexpected adverse events or safety concerns.

Interpretation: Our study indicates that at 12 months, IPE did not differentially affect weight gain, compared with the inulin control, in adults between 20 and 40 years of age, at risk of obesity.

Project: **LymeApp**

Title of paper: Lyme Disease General Practice Sentinel Scheme

Reference: British Journal of General Practice 2023; 73 (suppl 1): bjgp23X733569

Authors: Douglas et al

url: doi.org/10.3399/bjgp23X733569

Summary: **Background**: Lyme Disease (LD) is a multisystem zoonosis with uncertain epidemiology. It may be increasing in rural hotspots. GP datasets are weakened by coding and definitions. Public and climate concerns have raised awareness of LD.

Aim: Improving diagnostic coding, UK Lyme Disease incidence and distribution. Behavioural risk factors for public health policy.

Method: Education modules for 35 general practices from Orkney to Southampton; Remote installation of software providing decision support, case definitions, pictures, coding, prescribing guidelines; Questionnaire on tick exposure and removal methods; Anonymous data extraction; Data on tick bite body location, age, place of exposure, attachment time, removal methods, leisure pursuits and occupation to guide public health policy; GP data capture and coding from hospital, A&E and OOH (out of hours) records; Erythema Migrans (EM) is a clinical diagnosis without serological testing; Rash photographs; establish a data bank of disease expression in age groups, ethnicity, and skin types.

Results: There were 69 cases reported in the pilot period (September to December 2021), 52% diagnosed EM following a definite tick bite. Tick attachment time showed a majority > 24 hours, with home tweezers, fingernails often used for removal, with both associated with higher disease transmission. Analysis of pilot data suggested a Lyme Disease incidence of 94/100 000 with the inclusion of EM. This compares to a serologically confirmed incidence of 38.2/100 000 in 2019 in Highland Region.

Conclusion Early data suggests that the Lyme Disease General Practice Sentinel Scheme has improved case ascertainment, epidemiology, and risk factor understanding.

Project: **MISTY**

Title of paper: Comparison of intramyocellular lipid metabolism in patients with diabetes and male athletes

Reference: Nat Commun 15, 3690 (2024)

Authors: Mezincescu et al

url: https://doi.org/10.1038/s41467-024-47843-y

Summary: **Despite opposing insulin** sensitivity and cardiometabolic risk, both athletes and patients with type 2 diabetes have increased skeletal myocyte fat storage: the so-called “athlete’s paradox”. In a parallel non-randomised, non-blinded trial, we characterised and compared the skeletal myocyte lipid signature of 29 male endurance athletes and 30 patients with diabetes after undergoing deconditioning or endurance training respectively. The primary outcomes were to assess intramyocellular lipid storage of the vastus lateralis in both cohorts and the secondary outcomes were to examine saturated and unsaturated intramyocellular lipid pool turnover. We show that athletes have higher intramyocellular fat saturation with very high palmitate kinetics, which is attenuated by deconditioning. In contrast, type 2 diabetes patients have higher unsaturated intramyocellular fat and blunted palmitate and linoleate kinetics but after endurance training, all were realigned with those of deconditioned athletes. Improved basal insulin sensitivity was further associated with better serum cholesterol/triglycerides, glycaemic control, physical performance, enhanced post insulin receptor pathway signalling and metabolic sensing.

We conclude that insulin-resistant, maladapted intramyocellular lipid storage and turnover in patients with type 2 diabetes show reversibility after endurance training through increased contributions of the saturated intramyocellular fatty acid pools.

Project: **MOSAIC**

Title of paper: Multimorbidity in the Context Of Socioeconomic Deprivation: A mixed methods exploration of how Individual and Community factors interact to influence patient capacity to manage Multimorbidity (MOSAIC)

Reference: PhD thesis, University of Glasgow, Deposited April 2024

Authors: McCallum et al

url: https://theses.gla.ac.uk/84272/

Summary: Both individual and community factors have a critical impact on the capacity to manage multimorbidity, and some of these capacity factors are associated with mortality and hospital admissions. Burden of Treatment Theory (BOTT) constructs can be used to measure associations between capacity factors at the population level, and this could be built on to create a validated measure of capacity. Health services, and future interventions, should prioritise supporting and optimising person-centred care, work with communities to ensure services are authentic safe spaces and consider utilising peer support for people living with multimorbidity in areas of high socioeconomic deprivation. As community capacity shapes individual capacity, applying BOTT in the context of high socioeconomic deprivation without consideration of wider contextual, community factors, risks perpetuating and widening existing health inequalities. However, an extended BOTT incorporating community capacity, biography and being grounded could be utilised in a high socioeconomic deprivation context to help design health services and interventions for people living with multimorbidity. Such services have the potential to improve outcomes and narrow health inequalities in this setting.

Project: **Roshni 2**

Title of paper: Efficacy of a culturally adapted, cognitive behavioural therapy-based intervention for postnatal depression in British south Asian women (ROSHNI-2): a multicentre, randomised controlled trial

Reference: The Lancet, Volume 404, Issue 10461, 1430 – 1443, October 12, 2024

Authors: Husain, Nusrat et al

url: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)01612-X/fulltext

Summary: **Background**: Postnatal depression necessitates timely and effective interventions to mitigate adverse maternal and child outcomes in the short term and over the life course. British south Asian women with depression are often underserved and undertreated due to stigma, language barriers, and cultural barriers. This trial aimed to test the clinical efficacy of a culturally adapted, group cognitive behavioural therapy (CBT)-based intervention, the Positive Health Programme (PHP), delivered by non-specialist health workers for postnatal depression in British south Asian women.

Methods: This study was a randomised controlled trial, with culturally adapted recruitment and an internal pilot, comparing the PHP (intervention group) with treatment as usual (control group) in British south Asian women with postnatal depression. The study was conducted at five centres across the UK. Participants were aged 16 years or older, met the DSM-5 criteria for depression, and had infants aged 0–12 months. Randomisation (1:1) was stratified by centre, with a block size of 18, and was done through an independent remote telephone service. The PHP was delivered over 12 group sessions in 4 months. The primary outcome was recovery from depression (defined as a Hamilton Depression Rating Scale [HDRS] score ≤7) at 4 months after randomisation, and an assessment was also done at 12 months. Analysis was on an intention-to-treat basis including only participants with non-missing outcome data; we used a random-effects logistic regression model including fixed covariates for study site, baseline depression severity (HDRS score), parity, and years in education and a random coefficient for therapy group.

Findings: Of the 9136 individuals approached for recruitment between Feb 8, 2017, and March 29, 2020, 4296 women were eligible for and consented to screening, among whom 732 screened positive and were randomly allocated: 368 (50%) to the PHP group and 364 (50%) to the control group. Participants were mostly of Pakistani (397 [55%] of 719 with available data), Indian (176 [24%]), or Bangladeshi ethnicity (127 [18%]), with an overall mean age of 31·4 years (SD 5·2), with their youngest infants having a mean age of 23·6 weeks (14·2). At 4 months from randomisation, the proportion of participants who showed recovery from depression on the HDRS was significantly higher in the PHP group (138 [49%] of 281) than in the control group (105 [37%] of 281; adjusted odds ratio 1·97 [95% CI 1·26–3·10]). At the 12-month follow-up, this difference was no longer significant (1·02 [95% CI 0·62–1·66]).

Interpretation: In British south Asian women with postnatal depression, a culturally adapted group CBT-based intervention could aid in quicker recovery from depression compared with treatment as usual. Further research is needed to identify how to sustain the treatment effect and establish strategies for scale-up.

Project: **SOUL**

Title of paper: Novo Nordisk Company Announcement: Oral semaglutide demonstrates a 14% reduction in risk of major adverse cardiovascular events in adults with type 2 diabetes in the SOUL trial

url: See below

Summary: **21 October 2024** — Novo Nordisk today announced the headline results from the SOUL cardiovascular outcomes trial. The double-blinded, randomised trial compared oral semaglutide to placebo as an adjunct to standard of care for the prevention of major

adverse cardiovascular events (MACE). The trial enrolled 9,650 people with type 2 diabetes and established cardiovascular disease (CVD) and/or chronic kidney disease (CKD). As part of standard of care, 49% of patients received SGLT2i at some point during the trial.

The trial achieved its primary objective by demonstrating a statistically significant and superior reduction in MACE of 14% for people treated with oral semaglutide compared to placebo1. The primary endpoint of the study was defined as the composite outcome of the first occurrence of MACE defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. All three components of the primary endpoint contributed to the superior MACE reduction demonstrated by oral semaglutide.

In the trial, oral semaglutide appeared to have a safe and well-tolerated profile in line with previous oral semaglutide trials.

Novo Nordisk expects to file for regulatory approval of a label expansion for Rybelsus® in both the US and EU around the turn of the year. The detailed results from SOUL will be presented at a scientific conference in 2025.

About the SOUL trial

SOUL was a multicentre, international, randomised, double-blind, parallel-group, placebo-controlled, phase 3 cardiovascular outcomes trial with 9,650 people enrolled. It was conducted to assess the effect of oral semaglutide vs placebo on cardiovascular outcomes in people with type 2 diabetes and established CVD and/or CKD. The SOUL trial was initiated in 2019.

The key objective of SOUL was to demonstrate that oral semaglutide lowers the risk of major adverse cardiovascular events (a composite endpoint consisting of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) compared to placebo, both added to standard of care in patients with type 2 diabetes and established CVD and/or CKD.

About Rybelsus®: Oral semaglutide is administered once daily and is approved for use in three doses, 3 mg, 7 mg and 14 mg, under the brand name Rybelsus®. It is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise. In the EU, a new formulation of 1.5 mg, 4 mg and 9 mg doses of Rybelsus® are approved and are bioequivalent to the original formulation of Rybelsus®.

URL - https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=171480#:~:text=Novo%20Nordisk%20A%2FS%3A%20Oral,the%20SOUL%20cardiovascular%20outcomes%20trial

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Project: **UCON**

Title of paper: Ulipristal acetate versus levonorgestrel-releasing intrauterine system for heavy menstrual bleeding (UCON): a randomised controlled phase III trial

Reference: eClinicalMedicine 2023 May 18;60:101995

Authors: Whitaker et al

url: doi: 10.1016/j.eclinm.2023.101995

Summary: **Background**: Heavy menstrual bleeding affects one in four women and negatively impacts quality of life. Ulipristal acetate is prescribed to treat symptoms associated with uterine fibroids. We compared the effectiveness of ulipristal acetate and the levonorgestrel-releasing intrauterine system at reducing the burden of heavy menstrual bleeding, irrespective of the presence of fibroids.

Methods: This randomised, open-label, parallel group phase III trial enrolled women over

18 years with heavy menstrual bleeding from 10 UK hospitals. Participants were centrally randomised, in a 1:1 ratio, to either three, 12-week treatment cycles of 5 mg ulipristal acetate daily, separated by 4-week treatment-free intervals, or a levonorgestrel-releasing intrauterine system. The primary outcome, analysed by intention-to-treat, was quality of life measured by the Menorrhagia Multi-Attribute Scale at 12 months. Secondary outcomes included menstrual bleeding and liver function.

Findings: Between June 5th, 2015 and February 26th, 2020, 236 women were randomised, either side of a recruitment suspension due to concerns of ulipristal acetate hepatoxicity. Subsequent withdrawal of ulipristal acetate led to early cessation of recruitment but the trial continued in follow-up. The primary outcome substantially improved in both groups, and was 89, (interquartile range [IQR] 65 to 100, n = 53) and 94, (IQR 70 to 100, n = 50; adjusted odds ratio 0.55, 95% confidence interval [CI] 0.26–1.17; p = 0.12) in the ulipristal and levonorgestrel-releasing intrauterine system groups. Rates of amenorrhoea at 12 months were higher in those allocated ulipristal acetate compared to levonorgestrel-releasing intrauterine system (64% versus 25%, adjusted odds ratio 7.12, 95% CI 2.29–22.2). Other outcomes were similar between the two groups and there were no cases of endometrial malignancy or hepatotoxicity due to ulipristal acetate use.

Interpretation: Our findings suggested that both treatments improved quality of life. Ulipristal was more effective at inducing amenorrhoea. Ulipristal has been demonstrated to be an effective medical therapeutic option but currently its use has restrictions and requires liver function monitoring.