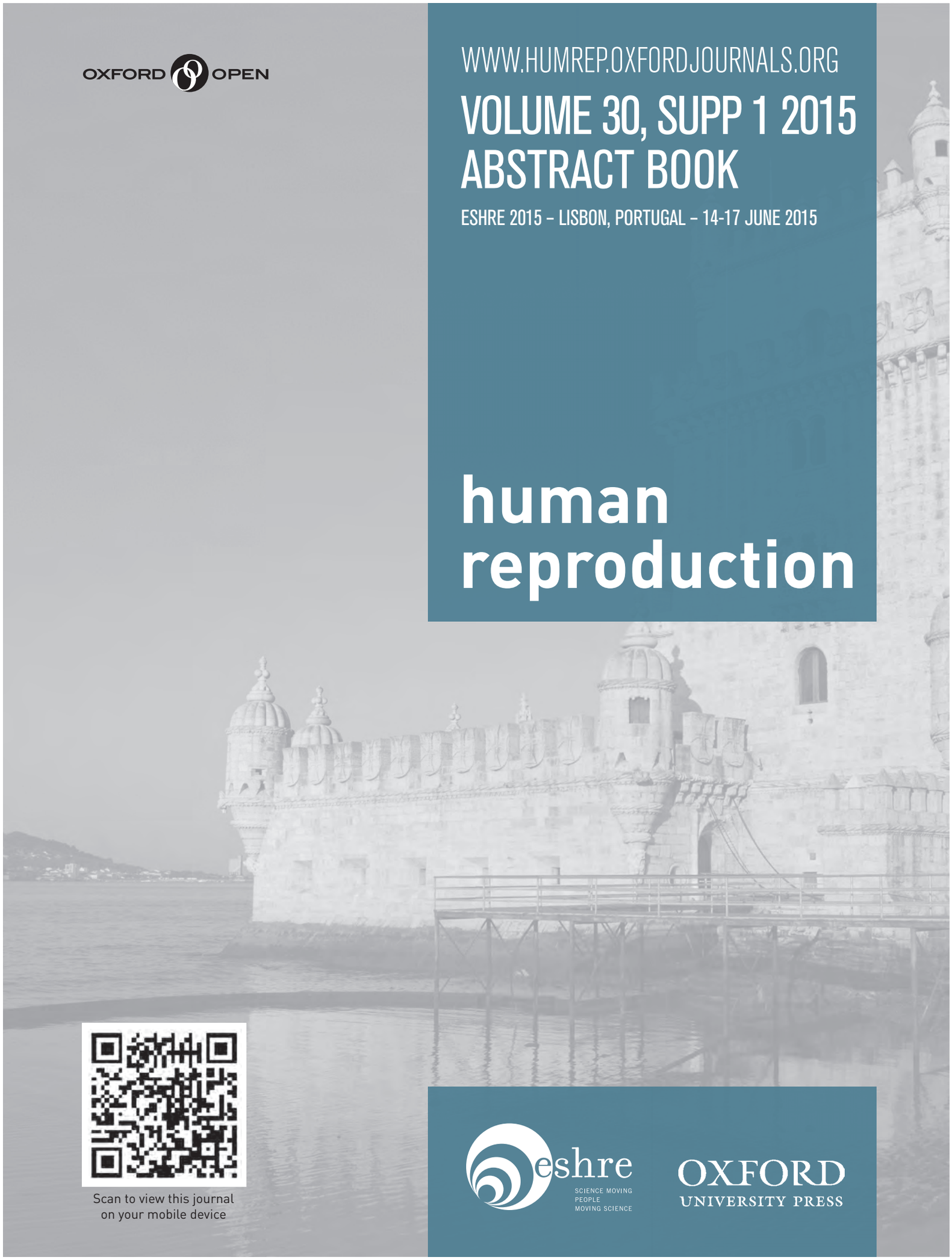

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VOLUME 30, SUPP 1 2015
ABSTRACT BOOK

ESHRE 2015 – LISBON, PORTUGAL – 14-17 JUNE 2015

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OXFORD UNIVERSITY PRESS

Abstracts of the 31st Annual Meeting of the European Society of Human Reproduction and Embryology

Lisbon

Portugal

14 to 17 June 2015

orthologues of which have been well characterized for their role in oogenic processes in animal models.
Limitations, reason for caution: The short read length used in our whole genome sequencing makes the detection of complex structural variants and repetitive regions more challenging.
Wider implications of the findings: The identification of rare, exonic and intronic genetic variants among our cohort highlights the power of whole-genome sequencing in the identification of variants that associate with altered human ovarian reserve. Our data emphasizes the complex, polygenic nature of ovarian reserve disorders and the likelihood that loci reportedly associated with these disorders represent only a small fraction of coding and non-coding loci regulating ovarian reserve.
Study funding/competing interest(s): Funding by commercial/corporate company(ies) – Celmatix Inc.
Trial registration number: NA.
Keywords: POI, ovarian reserve, next generation sequencing, genetics, infertility

O-023 Sirt2-mediated BubR1 regulation promotes oocyte maturation

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Study question: Does the sirtuin family member, Sirt2, positively influence oocyte maturation and what is its mechanism of action?
Summary answer: Sirt2 over-expression stabilizes BubR1 in mouse oocytes, promotes the formation of attachments between chromosomes and spindle microtubules and accelerates progression through meiotic maturation.
What is known already: Sirtuins (Sirt1–7) are a family of NAD^+-dependent deacetylases with diverse functions and potent anti-aging properties. In somatic cells, Sirt2 modulates a key cellular regulator known as BubR1 (for Budding uninhibited by benzimidazole-Related 1). BubR1-depletion disrupts meiotic progression in oocytes and the formation of attachments between chromosomes and spindle microtubules. It is unknown whether BubR1 is regulated by Sirt2 in oocytes and if this could be important for meiotic control.
Study design, size, duration: In order to examine the effect of increased Sirt2 levels, we engineered a transgenic mouse model of the C57BL/6J strain that over-expresses Sirt2 (hereafter referred to as Sirt2Tg). Fully-grown germinal vesicle (GV)-stage oocytes ($n > 30$ per group in triplicate) were isolated from hormonally-primed wild-type (WT) and Sirt2Tg mice.
Participants/materials, setting, methods: The timing of first polar body extrusion – which marks the completion of meiotic maturation – was assessed. High resolution confocal microscopy was used for detailed analyses of spindle assembly, chromosome alignment and sub-cellular localization of BubR1. Protein expression was quantified using Western blotting.
Main results and the role of chance: We used immunoblotting to compare Sirt2Tg oocytes with WT oocytes and confirmed that Sirt2Tg oocytes specifically over-expressed Sirt2 but not Sirt1. We found that Sirt2Tg females produced twice as many fully-grown oocytes as age-matched wild-type animals ($P < 0.05$). Significantly, Sirt2Tg oocytes expressed ~threefold higher levels of BubR1 than wild-type oocytes consistent with Sirt2-dependent BubR1 stabilization. Furthermore, at the sub-cellular level, BubR1 was enriched on spindle microtubules in Sirt2Tg oocytes. Importantly, spindle-localized BubR1 in transgenic oocytes was associated with accelerated formation of stable attachments between chromosomes and microtubules suggestive of increased meiotic efficiency. Entirely consistent with this, Sirt2Tg oocytes completed meiotic maturation marked by first polar body extrusion ~2 h in advance of WT oocytes.
Limitations, reason for caution: Although Sirt2 over-expression was associated with increased BubR1 and the observed effects inSirt2Tg oocytes are consistent with potentiated BubR1 function, Sirt2 could influence additional non-BubR1 targets that could also contribute to our findings.
Wider implications of the findings: Increased Sirt2 levels were associated with increased BubR1 stability and with effects consistent with potentiated BubR1 function, notably accelerated chromosome-microtubule attachment formation. Intriguingly, a recent paper examined the effect of Sirt2-depletion in mouse oocytes and reported impaired attachment formation between chromosomes and microtubules entirely in line with our results. Permeable small molecule Sirt2 agonists provide a novel prospect for impacting BubR1 function to improve oocyte quality.
Study funding/competing interest(s): Funding by University(ies). Funding by national/international organization(s) – UNSW MREII Grant. Ramaciotti Establishment Grant.
Trial registration number: NA.
Keywords: oocyte, meiosis, oocyte maturation, sirtuins, BubR1

O-024 Reproductive and metabolic effects of exogenous administration of irisin versus physical activity in high-fat diet-fed female mouse model

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Study question: Would the effects of physical activity and exogenous administration of irisin be similar or different on parameters related with reproduction and metabolism in the high-fat diet-induced obesity model of the female C57BL/6J mice? We hypothesized that exogenous administration of irisin would have similar affects as physical activity.
Summary answer: Exercise promotes weight-loss and healthy metabolism. It seems that irisin administration provides similar results compared to exercise in a female mouse model. Reproductive and metabolic parameters in blood showed similar improvements between exercise and irisin groups compared to controls. Moreover, ovarian histology presented comparable improvements after exercise and irisin administration.
What is known already: Obesity affects every aspect of reproduction in females, while exercise promotes healthy metabolism and protects against metabolic disorders like obesity. It has been documented that exogenously administered irisin (FNDC5), which is a new polypeptide hormone regulated by PGC1-alpha, induces the browning of subcutaneous fat and thermogenesis, and it presumably could be prepared and delivered as an injectable polypeptide. Indeed, increased formation of brown fat has been shown to have anti-obesity effects in adult humans.
Study design, size, duration: 60 female C57BL/6J mice were gathered at approximately 5–6 week of age and were divided into three groups. They were fed with a high-fat diet. Control group remained sedentary. Irisin group remained also sedentary but intravenously received 10^{10} FNDC5-expressing adenovirus after 20 weeks. Exercise group performed treadmill after 12 weeks.
Participants/materials, setting, methods: The study was carried out in an university hospital. Mice were killed at 22wk and had their ovaries excised for histological assessment. Blood was obtained by cardiac puncture. E2, FSH, LH, AMH, BMP, ANP, BNP, FGF21, ghrelin, insulin, leptin, adiponectin, resistin, kisspeptin, RBP4, visfatin levels were measured in blood.
Main results and the role of chance: Final weight, blood levels of estradiol (E2), follicle stimulating hormone (FSH), luteinizing hormone (LH), anti-mullerian hormone (AMH), bone morphogenetic proteins (BMP), atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), fibroblast growth factor 21 (FGF21), ghrelin, insulin, leptin, adiponectin, resistin, kisspeptin, retinol binding protein 4 (RBP4), visfatin were statistically similar between exercise and irisin groups ($p > 0.05$). Final weight, blood levels of BMP, FGF21, ghrelin, insulin, resistin, kisspeptin, visfatin were significantly lower in exercise and irisin groups compared to controls ($p < 0.05$), while LH/FSH ratio, ANP, BNP, RBP4 levels were significantly higher in the controls ($p < 0.05$). AMH level was significantly higher in exercise and irisin groups ($p < 0.05$). Ovaries of mice in exercise and irisin groups manifested different stages of follicular development, whereas the ovaries of mice in control group were inactive.
Limitations, reason for caution: Data of this study revealed that short treatments of obese female mice with irisin improved reproductive and metabolic parameters and caused a small weight loss. Whether similar or longer treatments with irisin and/or higher doses would cause similar or more weight loss in human subjects remains to be determined.
Wider implications of the findings: The therapeutic potential of irisin is apparent. Exogenously administered irisin induces the browning of subcutaneous fat and thermogenesis, and it presumably could be prepared and delivered

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