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Pre-pregnancy obesity and risk of congenital abnormalities of the kidney and urinary tract (CAKUT) – systematic review, meta-analysis and ecological study

Authors: Lyda Jadresić[1]* MBBS MD MSc, Howard Au[2]*, Christopher Woodhouse[3] MB FRCS FEBU, Dorothea Nitsch[4] MD MSc.

[1]Unaffiliated, retired consultant paediatrician from Department of Paediatrics, Gloucestershire Royal Hospital, Gloucester

[2]Medical student. University of Hong Kong.

[3]Emeritus Professor of Adolescent Urology, University College, London

[4]Professor of Clinical Epidemiology Department of Non-Communicable Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

*Joint first authors

ORCID numbers:

Lyda Jadresic: 0000-0002-3097-3175

Howard AU: 0000-0002-8194-4411

Christopher Woodhouse: 0000-0003-1276-2275

Dorothea Nitsch: 0000-0001-5767-248X

Corresponding Author: Dr Lyda Jadresić, email address: lydajadresic@hotmail.com

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ABSTRACT:

INTRODUCTION: There is increasing evidence that maternal obesity is associated with several structural birth defects. Congenital abnormalities of the kidney and urinary tract (CAKUT) account for 30 to 50% of children starting kidney replacement therapy (KRT). We conducted a systematic review, meta-analysis and ecological study to explore the relationship between maternal obesity and CAKUT.

METHODS: A systematic literature search was conducted in EMBASE, MEDLINE, Global Health, The Cochrane Library, Scopus and Web of Science. Study quality was assessed for bias and confounding. A meta-analysis using a random effect model was carried out to obtain a summary odds ratio (OR) and 95% confidence interval (CI). In the ecological study, country level data were used to examine the correlation of secular trends in female obesity, CAKUT incidence and incidence of KRT.

RESULTS: Eight epidemiological studies were included in the review, 4 cohort studies and 4 case-control studies, 7 of which were included in the meta-analysis. There was evidence of a positive association between obesity during pregnancy and the risk of CAKUT, with a summary OR = 1.14 (1.02 – 1.27). No association was seen with overweight, nor a dose response with increasing obesity. There was an increasing trend in countries' proportion of female obesity and an increasing trend in reported CAKUT incidence with specific rises seen in congenital hydronephrosis (CH) and multi-cystic kidney dysplasia (MCKD).

CONCLUSION: Our findings suggest that pre-pregnancy obesity may be associated with increased risk of CAKUT at population level.

Key words: pre-pregnancy obesity; CAKUT (congenital anomalies of the kidney and urinary tract); meta-analysis; systematic review; ecological study

INTRODUCTION:

Obesity is a major public health issue and its prevalence continues to rise worldwide[1]. There is increasing evidence that maternal obesity is associated with several structural birth defects[2-4]. Congenital abnormalities of the kidney and urinary tract (CAKUT) account for 30 to 50% of children starting KRT[5] and occur in around 0.4 to 4 per 1000 pregnancies [6,7]. Although milder forms of CAKUT can remain asymptomatic, others will give rise either in infancy or later in life to recurrent urinary tract infections, hypertension or kidney insufficiency[6,8]. CAKUT is often an isolated condition with gene abnormalities accounting for approximately 15% of cases[9], can occur in families and in hundreds of syndromes[10]. Variations of the CAKUT phenotype within families and the variable expressivity of CAKUT-causing genes point to environmental factors, maternal obesity being one of them [9]. Animal studies have shown that maternal hyperglycaemia and maternal obesity can affect kidney development in the offspring[11,12]. Maternal type 1 diabetes mellitus (DM) and gestational DM (GDM) are known to increase the risk of congenital malformations[13,14] including CAKUT[15]. The effect of maternal obesity on CAKUT is less well known with studies showing different results[16,17].

The aim of this study was to systematically review the evidence and pool data that examined the association of obesity during pregnancy and CAKUT. As a secondary aim we conducted an ecological study to examine population trends in maternal obesity and incidence of CAKUT.

MATERIALS and METHODS

Systematic Review and Meta-Analysis:

These were conducted following PRISMA guidelines[18]. The protocol is registered on PROSPERO (PROSPERO ID 121709).

Criteria for inclusion were that studies were conducted in humans, had obesity as the defined exposure, indicated congenital abnormalities as an outcome, had a direct control group, were published in English and were peer-reviewed.

The literature search was conducted up to November 2018 using EMBASE (from 1947), MEDLINE (from 1879), Global Health (from 1973), The Cochrane Library (from 1996), Scopus (from 2004) and Web of Science (from 1900).

Searches using free-text and MeSH terms were done and the domains were obesity, pregnancy, congenital anomalies/abnormalities and birth registry or medical records, in order to identify studies on large populations with sufficient number of CAKUT outcomes (Supplementary File (SF) A). Under the domain "congenital abnormalities, we included: CAKUT, Vesico-ureteric/vesico-ureteral reflux, Renal/kidney dysplasia, Renal/kidney dysgenesis, Renal/kidney agenesis, Renal/kidney hypoplasia, Multicystic kidney dysplasia (MCD), Obstructive urinary defect, Obstructive genito-urinary defect, Megaureter, Pelvic ureteric, Hydronephrosis, Posterior urethral valves, Renal abnormality/anomaly, Urinary abnormality/anomaly, Kidney abnormality/anomaly, Renal/kidney cysts/cystic.

Study selection

Duplicates were removed. All titles and abstracts were examined by one reviewer (HA). Full text searches were made looking for urinary/kidney abnormalities if these were not mentioned in the abstract. A sample of 100 references were selected randomly and evaluated by a second reviewer (DN). There was full agreement.

Data collection process

A predesigned form was used to record extracted data that included study design, author name, year, setting, study population, CAKUT abnormality, definition of obesity and obesity subgroups, ascertainment, selection of control group, number of CAKUT cases in non-obese and in obese groups, crude and adjusted odds ratio (OR) and 95% confidence intervals (95%CI) and confounders.

Quality assessment

Risk of bias was assessed by HA, DN and LJ, using the following criteria: selection bias, information bias in the measurement of pre-pregnancy BMI and in the diagnosis and ascertainment of CAKUT cases. Study quality was further assessed by looking at adjustment for key confounders: maternal age, race/ethnicity, smoking, maternal diabetes status, folic acid use and socioeconomic status: maternal education, maternal parity (SF B for other desirable confounders). Studies were assigned high risk, low risk or uncertain according to the above criteria and were colour coded.

Meta-analysis

The main exposure was maternal obesity at time of conception or during the first trimester of pregnancy ("pre-pregnancy obesity"). The outcome was any form of CAKUT as defined in individual studies. Meta-analysis was performed in studies containing the OR or risk ratio (RR), comparing the incidence of CAKUT in maternal obese group and in non-obese group. If a study only reported a risk ratio for CAKUT for different levels of obesity, each measure of effect was included in the meta-analysis, otherwise we used the overall measure. The standard error for each study was calculated from log OR and log 95% CI. A pooled adjusted OR and 95% CI across studies was computed using a random effects model using Stata version 13 (www.stata.com). A subgroup analysis was carried based on study design. The

data were displayed in forest plots. We also obtained a pooled estimate for the association between CAKUT and obesity subclasses and overweight.

Heterogeneity was quantified by calculating I^2, classified as 0-40% = might not be important; 30-60% = moderate; 50-90% = may represent substantial heterogeneity; 75-100% = considerable heterogeneity [19]. To exclude the possibility that a study exerted excessive influence on the heterogeneity, we conducted a sensitivity analysis by omitting 1 study at a time. We assessed the presence of publication bias using funnel plots and the Egger test where a p value of less than 0.10 was interpreted as supporting publication bias.

Ecological study

The main exposure for the ecological study was the countries' age standardised prevalence (ASP) of obesity per year in women aged 18 years or older. Obesity was defined as a BMI of 30 or above. We used the data published by the WHO (SF C). Other country level exposures explored were the ASP of raised fasting blood glucose and smoking in females, countries' gross domestic product (GDP), inequality using the GINI index. Outcome data consisted of a) the annual incidence per country of CAKUT (overall and specific diagnosis), data derived from EUROCAT[20], a European network of population-based registries for the surveillance of congenital abnormalities where cases are classified based on ICD10 with the British Paediatric Association extension and include livebirths, foetal deaths from 20 weeks gestational age and terminations of pregnancy for foetal anomaly at any gestation. The urinary abnormalities included in EUROCAT's surveillance are: bilateral kidneyagenesis, MCKD, congenital hydronephrosis (kidney pelvis diameter ≥ 10mm after birth), bladder exstrophy, posterior urethral valves and/or prune belly) b) the annual proportion per country of CAKUT as the primary kidney pathology in children under 15 years entering RRT in European countries derived from ERA-EDTA data and c) the incidence per country of young

people below 21, 18 or 16 years having RRT. Please seeSF C for RRT and other country level sources.

RESULTS

Systematic review

We initially identified 2107 articles. After removal of duplicates 1417 articles remained. Forty-five studies met our criteria and after assessment of their full text, 37 were excluded (Figure 1, SF D). The number of studies retrieved from each database is given in SF E. Eight studies were left after exclusions: 4 cohort studies (Block[17], Blomberg[21], Garcia-Patterson[22] and Persson[23]) and four case-control studies (Honein[24], Oddy[25], Slickers[16] and Tromp[26]), see Table 1.

Exposure Definition:

Obesity was defined using the WHO classification of BMI, as a BMI≥30 [27] in all studies except Garcia-Patterson which used BMI tertiles, upper tertile was a BMI of 24.78-47.07. This was similar to the "high BMI" group in the Honein study (BMI ≥ 25). Three cohort studies (Block, Blomberg and Persson) further subdivided obesity into 3 WHO subclasses (Class I: BMI ≥ 30 ≤ 35, Class II: BMI ≥ 35 ≤ 40 and Class III: BMI ≥ 40)[28] ; Block and Persson provided effect measures for obesity and for the specific subclasses of obesity, Persson provided these for each subclass only. Except for the Honein study, the rest of the studies provided a separate effect measure for overweight; this corresponded to the 2nd tertile in the Garcia-Patterson study. All but one study used the pre-pregnancy weight as recollected by the mother for the pre-pregnancy BMI calculation. The Persson study used early pregnancy BMI using measured weight at the first antenatal visit in the first trimester.

Outcome Definition:

The diagnosis of CAKUT was based on the International Classification of Diseases, edition 9 or 10 in all studies except for the Garcia-Patterson which used a non-standardised definition. The outcome was reported with all CAKUT diagnoses grouped together under "Urinary Abnormalities" using ICD-9 or 10 codes in Persson and Oddy, without further details, excluding known chromosomal, genetic or syndrome diagnoses. Garcia-Patterson grouped them as Renal/Urinary without further details. The rest of the studies provided definition of outcomes giving details of the specific diagnoses included. Persson had a separate Genital abnormalities outcome. Garcia-Patterson and Oddy didn't and it is possible that minor anomalies, especially hypospadias, were included. Specific CAKUT diagnoses were used as outcome in Block (Obstructive Genito-Urinary Defect, Renal Agenesis (RA)/hypoplasia) and in Blomberg (Cystic kidney, RA/hypoplasia), in Honein (RA/Hypoplasia, Obstructive defects, Renal or Ureter duplication), in Slickers (RA/Hypoplasia), in Tromp (Bilateral RA, MCD, congenital hydronephrosis (kidney AP≥ 10 mm), bladder exstrophy or epispadias, posterior urethral valves or prune belly syndrome).

The age at diagnosis of CAKUT was at birth or in the neonatal period in Blomberg, Persson and Garcia-Patterson, by 1 year of age in Block, Honein and Slickers, by 6 years of age in Oddy and by 10 years of age in Tromp.

Quality Assessment:

Cohort studies: There were four cohort studies, two from Sweden (Blomberg and Persson) which were nationally based, one from Spain, based at a hospital in Barcelona (Garcia-Patterson) and a regional study in the USA (Block) based in Florida (Table 1). The total sample size consisted of 3419969 pregnancies and 9459 CAKUT cases. The populations in Block, Blomberg and Persson were over a million with hundreds of cases, in contrast to the

small cohort in Garcia-Patterson with just over two thousand participants. The study periods span the years from 1986 to 2014. Blomberg, Block and Persson excluded known chromosomal syndromes; in addition, Persson excluded infants with genetic or malformation syndromes as well as congenital viral infections linked to malformations. This is unknown for the Garcia-Patterson study.

Only Block excluded mothers with pre-existing diabetes but included GDM. Blomberg and Persson included both types. GDM was included in all studies and was present in 7,5% of obese mothers in Block, not stated in the others. Only Persson carried out a sensitivity analysis excluding all diabetes which showed no difference in the estimate. Garcia-Paterson studied high BMI in mothers with GDM.

Case-control studies: The four case-controlled studies originated from Australia (Oddy), the USA (Honein and Slickers) and from the Netherlands (Tromp) (Table 1). There was a total of 765 cases and 5616 controls. The oldest study is Honein with data from 1968 to 1980. The three other studies have data from 1997 to 2010. Cases were identified from regional or state level registries and included CAKUT occurring in live births, stillbirths and foetal deaths. Cases with known chromosomal abnormalities were excluded. Controls were selected from healthy infants born in the same area and period of time as the cases except for Tromp where controls were live infants or foetuses with a known syndrome, chromosomal or monogenic anomaly. Slickers and Honein excluded mothers with pre-existing diabetes. Oddy performed a sensitivity analysis which showed no difference. GDM was excluded by Honein and adjusted for by Slickers but not by Oddy or Tromp and was present in 1.2% of obese women in the Tromp study, not stated in the others.

See Table 2 for summary of quality criteria and assessment (details in SF F). Overall, the quality of cohort studies was higher showing low selection bias through the use of population-based

birth registries with the exception of Garcia-Patterson where the selection process was uncertain. There was a lack of detail on the conditions of the exposure measurement in Block and Garcia-Patterson. Measurement of the outcome was mostly unbiased helped using birth registries which had defined diagnostic classification and the use of defined age of ascertainment of the diagnosis of CAKUT, except for the Blomberg study where this varied from birth to 13 years of age. In all but one study there was an acceptable level of adjustment for confounders.

The case-control studies had a high risk of information bias arising from the use of self-reported maternal pre-pregnant BMI obtained after the outcome and at various times after birth. Adjustment for key confounders was poor in two and adequate in two studies. The effect estimate was higher in case-control studies, which also had wider confidence limits.

Meta-analysis

García-Patterson study was excluded from the meta-analysis because it was conducted amongst women with GDM, which is on the causal pathway between BMI (the exposure of interest) and CAKUT. This left 4 case control studies and 3 cohorts.

The individual study ORs were of similar order of magnitude with considerable overlap of 95% CI (Figure 2). The results indicated a positive association between pre-pregnancy obesity and CAKUT with an overall pooled OR of 1.14 (1.02 – 1.27). There was a moderate degree of heterogeneity with an I^2 of 51.5%, p=0.024, with the Persson study explaining most of the heterogeneity. When this study was omitted the OR was 1.23 (1.09-1.39) I^2=26.7%, p=0.216. Omitting the Honein paper (which grouped together overweight and obese) from the obese group resulted in a very minimal increase in the summary estimate (see SF G). The subgroup cohort summary estimate was smaller and had narrower 95% CI

than the that of case-control studies although there was low statistical evidence of a difference (p=0.06). There was no clear evidence of a "dose-response" effect with increasing Obesity (SF H). There was no association with overweight, pooled OR was 1.02 (0.97 – 1.07), I^2 = 0.0%, p=0.958 (SF I). Neither the funnel plot nor the Egger test suggested publication bias (SF J).

Ecological study:

Data from 21 European countries from 1980 show an upward trend in female obesity (Figure 3) which coincides with an increase in the yearly incidence of CAKUT (Figure 4). When the relationship with female obesity is examined in more detail for specific CAKUT diagnoses, only the incidence of Congenital Hydronephrosis and of MCKD seem to increase whilst the other two remain stable[20] (SF K). Individual country plots of proportion of female obesity against each specific CAKUT diagnosis seemed to confirm this pattern (SF L). There was no increase in the proportion of children with a CAKUT diagnosis entering KRT when looking at European data from 1980 onwards (SF M-a). We then explored whether secular trends in children starting KRT mirrored the increase in female obesity. We assumed that the proportion entering KRT with a CAKUT diagnosis would remain the same in each country over the period studied. Using data from a wide range of countries worldwide on the yearly incidence of all children starting KRT from the late 1990s we found that there was no overall proportional increase (SF M-b). The only country where the RRT incidence (in < 25-year olds) mirrored the increase in female obesity was Malaysia. There were no associations between ASP of female smoking and glycaemia, countries' GDP or Gini index (SF N

DISCUSSION

In this study, we have We found that maternal obesity may be a risk factor for CAKUT. The meta-analysis showed a small but positive association between pre-pregnancy obesity and CAKUT. This was not seen with overweight in pregnancy nor did we find a dose response with increasing obesity. The size of the association is similar to the level of risk found in comparable meta-analysis of pre-pregnancy obesity and other congenital defects[4].

The results of the ecological study suggested that as female obesity increased so had the overall number of CAKUT diagnoses.

The mechanisms for this association are not clear. Maternal obesity is associated with a wide range of metabolic abnormalities, but little is known about their potential effect epigenetic effects.[29]

Our results were mainly driven by papers based on large-population birth registries with most studies using external, well standardised definitions of the exposure and outcome. Cohorts and case-control studies were characterised by low selection bias since data were mainly obtained from birth registries and by low bias in assessing the outcome. Most studies had adjusted for key confounders, and therefore this small association seen may be potentially real.

Our study suffers from some limitations. We conducted the meta-analysis on aggregated data rather than individual data. However, the absolute number of participants and events was very high and therefore the summary estimate is likely to be similar with either method[30,31]. In the studies included in the meta-analysis, there was clinical heterogeneity arising from differences in outcomes definitions, with CAKUT diagnoses either grouped together or analysed individually. Grouping may have increased the power of these studies but this may not be the right approach as the risk may vary depending on the specific

CAKUT diagnosis. There was some suggestion from the ecological study that only congenital hydronephrosis and MCKD showed increases as female obesity increased.. Confounding by pre-existing diabetes was adequately addressed except for one study (Bloomberg). All studies in the meta-analysis except Honein's included infants of mothers with GDM which may lie in the causal pathway between obesity and CAKUT. Only Persson performed a sensitivity analysis excluding GDM mothers. Slickers adjusted for GDM; however, if GDM lies in the causal pathway, this adjustment would probably result in a lower estimate. However, where available, the proportion of obese women with GDM was very small. The association of gestational DM and CAKUT was independent of pre-pregnancy BMI[15]. Although our results would suggest that pre-pregnancy BMI may have a threshold effect on kidney development, the absence of a dose related effect might be due to small numbers of CAKUT outcomes in the obesity sub-categories. The ecological study may be showing secular increases in the ascertainment of CAKUT related to increased reporting, for example of mild congenital hydronephrosis, or to the greater availability of prenatal ultrasound, occurring in parallel to increases in female obesity. This explanation, however, is less likely to apply to conditions such as MCKD, which shows definitive and more obvious features on prenatal ultrasound. . The findings from the ecological study showing secular, parallel increases in female obesity and in the diagnoses of congenital hydronephrosis and MCKD should not be used to interpret individual risk and should instead be regarded as sources for hypotheses to be tested in further studies. Diagnosis evident at birth rely on prenatal ultrasound findings, usually performed by 20 weeks gestation. CAKUT may become apparent later in gestation and ultrasonography is technically more difficult in obesity, conceivably missing a CAKUT diagnosis altogether. CAKUT may become apparent later in life and may be underdiagnosed in young adults presenting in CKD stage 5[32]. This differential

bias would underestimate the effect of maternal obesity. Case-control studies had wider 95% CI and their use of self-reported pre-pregnancy weight increased information bias. The cohort sub-estimate, although smaller, may be more accurate. There is a lack of studies from middle- and low-income countries.

Implications:

This increase in risk, even though small, needs to be seen as potentially adding to the burden of disease linked to pre-pregnancy obesity such as increased risk of other congenital abnormalities as already mentioned and increased risk in long term obesity and increased cardiometabolic risk in the offspring[33,34]. There is a public health dimension to the findings of our study because obesity continues to rise worldwide, especially in females[1]. Management of obesity at the start of antenatal care may be too late because the first glomeruli form between 9 to 10 weeks gestation and the kidney development will have completed its morphological changes by 20 weeks. Public health measures that address the obesogenic nature of living environments are going to be more effective.

The association found is small and it is not possible at this stage to be certain about the clinical implications of our findings on an individual context beyond continuing being proactive on encouraging a healthy lifestyle in our paediatric patients.

This association should be the subject of further studies in different populations, focussing on specific CAKUT diagnoses.. The importance of birth registries in this context is paramount. The impact of the associations seen may be greater in settings where there is poor or no access to paediatric urological care. Further research on potential mechanisms to explain this association is needed.

Conclusions

Our analysis suggests that pre-pregnancy obesity may be a risk factor for CAKUT, but this finding needs to be explored further within specific CAKUT diagnoses.

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Table 1. Characteristics of eligible studies

Cohort studies:								
			Obesity		*CAKUT*			*Confounders adjusted*
Study	*Setting*	*Population*	*Definition*	*Ascertained*	*Definition*	*Specification*	*Ascertained*	
Block 2013	*Florida, USA*	*Florida resident mothers without pre-gestational diabetes who gave birth to live singleton infants from March 2004 through December 2009 (1,124,370 infants, 3987 cases of Obstructive Genito-urinary Defect, 435 cases of renal agenesis /hypoplasia)*	*WHO classification based on BMI[35]: Underweight: <18.5 Normal: 18.5-24.9 Overweight: 25.0-29.9 Obese I: 30.0-34.9 Obese II: 35.0-39.9 Obese III: ≥ 40.0*	*FBDR (Florida Birth Defects Registry) – modified to capture maternal pre-pregnancy weight and height in 2014*	*Obstructive genito-urinary defect and renal agenesis/hypoplasia based on ICD-9 codes*	*As per Definition column*	*FBDR, diagnosed within 1st year of life, excluding trisomies 21, 18 and 13*	*Maternal age, race/ethnicity, education, smoking, marital status, and nativity.*
Blomberg 2010	*Sweden*	*Mothers resident in Sweden giving birth to live infants or*	*WHO classification based on BMI*	*Swedish medical birth register (based on standardised*	*ICD-9 codes 740.0–759.9 or ICD-10*	*Kidney agenesis/dysge*	*Swedish Medical Birth Registry and the Swedish Register of Birth Defects both based on data from*	*Maternal age, parity, smoking in*

		stillbirth (after 28 weeks gestation) between January 1, 1995, through December 31, 2007 with Diabetes included (1,049,582 infants, 291 cases of kidney agenesis/dysgenesis 391 cases of cystic kidney)	*including Obesity classes I to III*	*medical record forms completed at the maternity health care centres at the start of prenatal care, usually in gestational week 10–12)*	*codes beginning with Q*	*nesis, cystic kidney .*	*the neonatal period including stillbirths from 28 weeks gestation and from the National Patient Register which contains information on discharge diagnoses of all patients admitted to Swedish hospitals and was used up to and including 2007. Age at diagnosis from birth to up to 13 years of age. It excluded infants with known chromosomal abnormalities*	*early pregnancy, and year of birth*
García-Patterson 2004	*Barcelona, Spain*	*mothers with a documented diagnosis of Gestational Diabetes Mellitus who gave birth to liveborn between January 1986 and July 2002 at ≥22 complete weeks of gestation at a single institution (Hospital of the Holy Cross and St Paul,*	*BMI grouped into tertiles:* *15.43-21.91* *21.92-24.77* *24.78-47.07*	*Not mentioned*	*Neonatologist assessment before hospital discharge, classified into Major Congenital Malformation if caused significant functional or cosmetic impairment or required surgery or Minor if not*	*Renal/Urinary .*	*Not mentioned, possibly from Hospital records before discharge after birth*	*Previous hyperglycaemia, parameters related to severity of GDM, pre-pregnancy BMI, maternal age, maternal smoking*

		Barcelona, Spain), 2060 infants, number of cases not provided			*serious medical/cosmetic significance and occurring in <4% of the background population.*			
Persson 2017	*Sweden*	*Mothers resident in Sweden giving birth to liveborn singleton infants from 2001 to 2014 with diabetes included (1,243,957 infants, 4211 cases of Urinary malformations)*	*WHO classification based on BMI including Obesity classes I to III*	*Swedish medical birth register, based on measured weight and self-reported height in first trimester at health care centres*	*ICD-10 classification and were defined according to the European Surveillance of Congenital Anomalies classification*	*Urinary malformations*	*Swedish medical birth register using standardised prenatal, obstetric, and neonatal records, the national patient register, cause of death register and total population register which includes diagnoses and dates on visits for hospital based inpatient and outpatient care, diagnosed by 1 year of age. Exclusions: infants with chromosomal aberrations, genetic syndromes, malformation syndromes with known causes, and viral infections having a possible association with malformations.*	*Maternal age (13-24, 25-29, 30-34, ≥35 years), height (130-154, 155-159, 160-164, 165-169, 170-174, 175-200 cm), parity (primiparous, multiparous), early pregnancy smoking status (non-smoker, 1-9, ≥10 cigarettes daily), educational level (<10, 10-12, >12 years), maternal country of birth (Nordic (Sweden,*

								Denmark, Finland, Iceland, and Norway), non-Nordic), family situation (living with partner, not living with partner), and sex of offspring
Case--control studies:								
			Obesity		*CAKUT*		*Control*	*Confounders adjusted*
Study	*Setting*	*Population*	*Definition*	*Ascertained*	*Definition*	*Specification*	*Selection*	
Honein 2003	*Atlanta, USA*	*Infants born in the five-county metropolitan Atlanta area during 1968 –1980, excluded if mother had diabetes* *Cases = 169* *Controls = 2763*	*National Institutes of Health[36] BMI classification then grouped as:* *high BMI = ≥ 25* *low BMI = < 25*	*Interviewed by telephone in 1982 and 1983 (pre-pregnancy weight and height), BMI calculated by clinician*	*Hospital Adaptation of the International Classification of Disease (H-ICDA) or ICD-9 classification*	*Congenital kidney anomalies: agenesis/hypoplasia, Obstructive defects, kidney or ureter duplication.*	*Identified by the Centres for Disease Control and Prevention's population-based surveillance system and the Metropolitan Atlanta*	*Control-infants were randomly selected from live births to residents of metropolitan Atlanta, and were frequency-matched to case-infants according to birth year,*	*gravidity, sex, birth weight, gestational age, maternal education, maternal age, and maternal smoking*

							Congenital Defects Program (MACDP)	*race, and birth hospital*	
Slickers 2008	*USA*	*Infants born between 1997 and 2003 in Arkansas, California, Iowa,* *Massachusetts, New Jersey, New York, Texas and Atlanta (liveborn or liveborn and foetal deaths depending on state), excluded if mother had pre-pregnancy Diabetes* *Cases = 75* *Controls = 868*	*WHO classification based on BMI*	*Structured computer-assisted telephone interviews within 24 months of delivery*	*ICD-9 based diagnosis of bilateral kidney agenesis or hypoplasia. Exclusion of single-gene conditions and chromosomal abnormalities*	*Bilateral kidney agenesis or hypoplasia diagnosed up to the first year of life*	*National Birth Defects Prevention Study formed by eight states which have ongoing population-based birth defects surveillance systems diagnosed within 1st year of life*	*Randomly selected at each study centre by using birth files or hospital records*	*Study centre, maternal education (≤12 or >12 years), maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), maternal age (years), the presence or absence of hypothyroidism, gestational diabetes, subfertility as determined by maternal question of whether either parent required or*

									sought assistance for pregnancy through medications or procedures, late pregnancy identification (after 12 weeks), vasoactive substance use during the first trimester, and a continuous representation of the number of months that folic acid was used during this 4-month periconceptional period
Oddy 2009	*Australia*	*Infants (live births, stillbirths and terminations of pregnancy) between September*	*WHO classification based on BMI*	*Self-reporting questionnaires*	*Diagnoses based on ICD-9 with British Association extension Malformation*	*Urinary malformation*	*Western Australian Birth Defects Registry*	*A random sample of all live born infants in Western Australia using the*	*Marital status, maternal age, maternal education and periconceptional*

		1997 and March 2000. Cases = 87 *Controls = 418*			*ascertained by four months after birth/termination, excluding cases with a known chromosomal, genetic or syndrome*			*statutory Midwives' Notification System of all births in Western Australia as a sampling frame*	*folic acid supplementation.*
Tromp 2012	*Northern Netherlands*	*Children and foetuses born between 1997 and 2010 and included live births, foetal death, stillbirths, miscarriages and elective terminations, no exclusions related to maternal pre-pregnancy or gestational Diabetes* *Cases 434* *Controls 1567*	*WHO classification based on BMI including Obesity classes I to III*	*EUROCAT Northern Netherlands database*	*ICD10 with the British Paediatric Association (BPA) one-digit extension*	*Urinary abnormalities: Bilateral kidney agenesis, multicystic kidney dysplasia, congenital hydronephrosis (kidney AP≥ 10 mm), bladder exstophy or epispadias, posterior urethral valves or prune belly syndrome*	*EUROCAT Northern Netherlands database*	*Children and foetuses born between 1997 and 2010 with a syndrome, chromosomal or monogenic anomaly*	*Maternal age at delivery, smoking, education, folic acid use and history of pregnancy affected by congenital anomalies*

Table 2: Summary of quality assessment: green = low risk, yellow = uncertain risk, red = high risk of bias or confounding

Cohort studies									
	Selection bias	*Information Bias (Exposure)*			*Information Bias (Outcome)*				*Confounding*
Study	*Loss to follow up*	*Non-differential misclassification of exposure*	*Recall bias*	*Observer bias*	*Non-differential misclassification of outcome*	*Recall bias*	*Observer bias*	*Ascertainment bias*	*Confounding*
Block									
Blomberg									
García-Patterson									
Persson									

Case-control studies										
Selection Bias			*Information Bias (Exposure)*			*Information Bias (Outcome)*				*Confounding*
Study	*Loss to follow up*	*Selection of control*	*Non-differential misclassification of exposure*	*Recall bias*	*Observer bias*	*Non-differential misclassification of outcome*	*Recall bias*	*Observer bias*	*Ascertainment bias*	*Confounding*
Honein										
Oddy										
Slickers										


Tromp

Figure 1. Flow of study selection into systematic review/meta-analysis

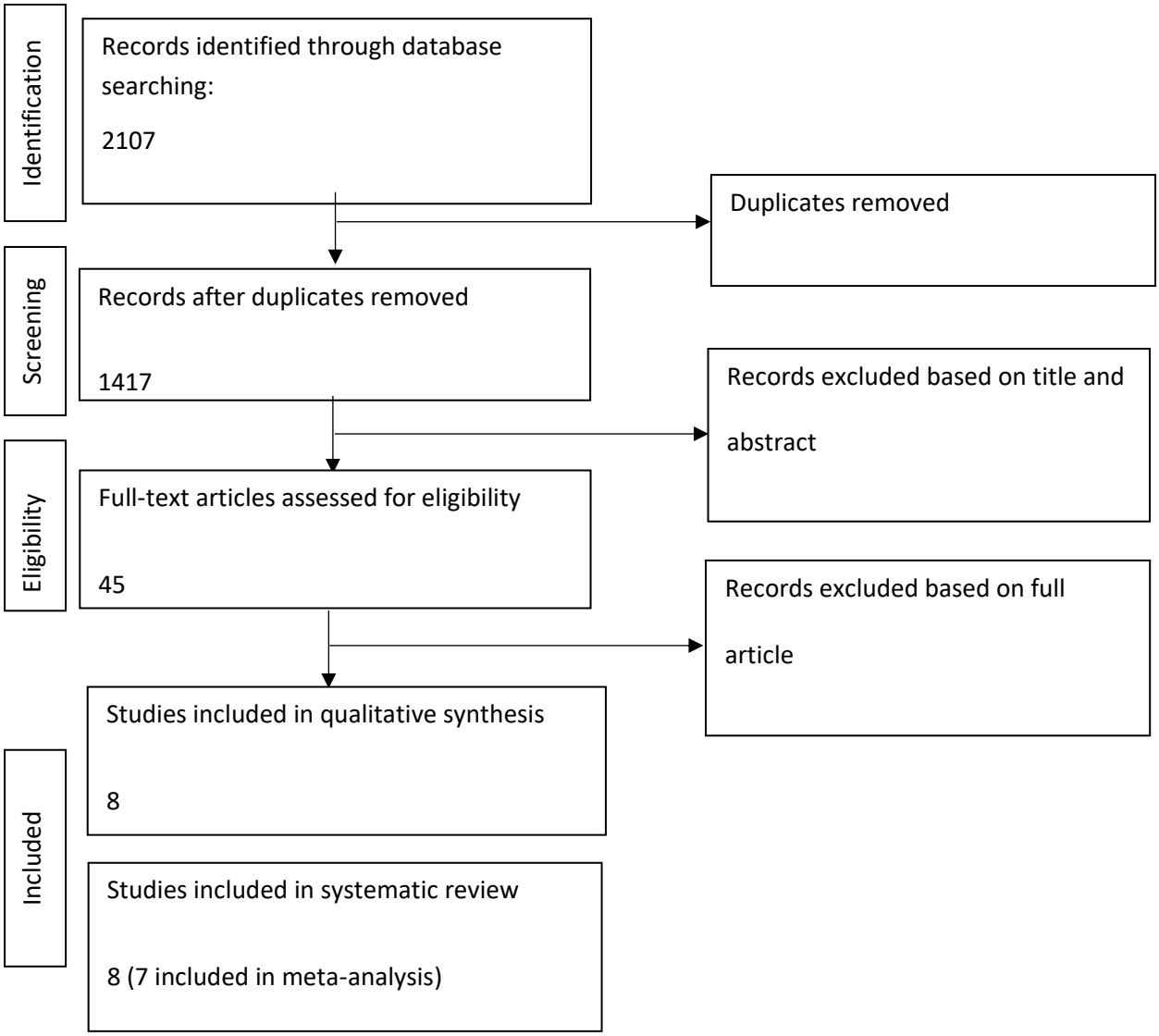

Figure 2: Forest Plot CAKUT and pre-pregnancy obesity

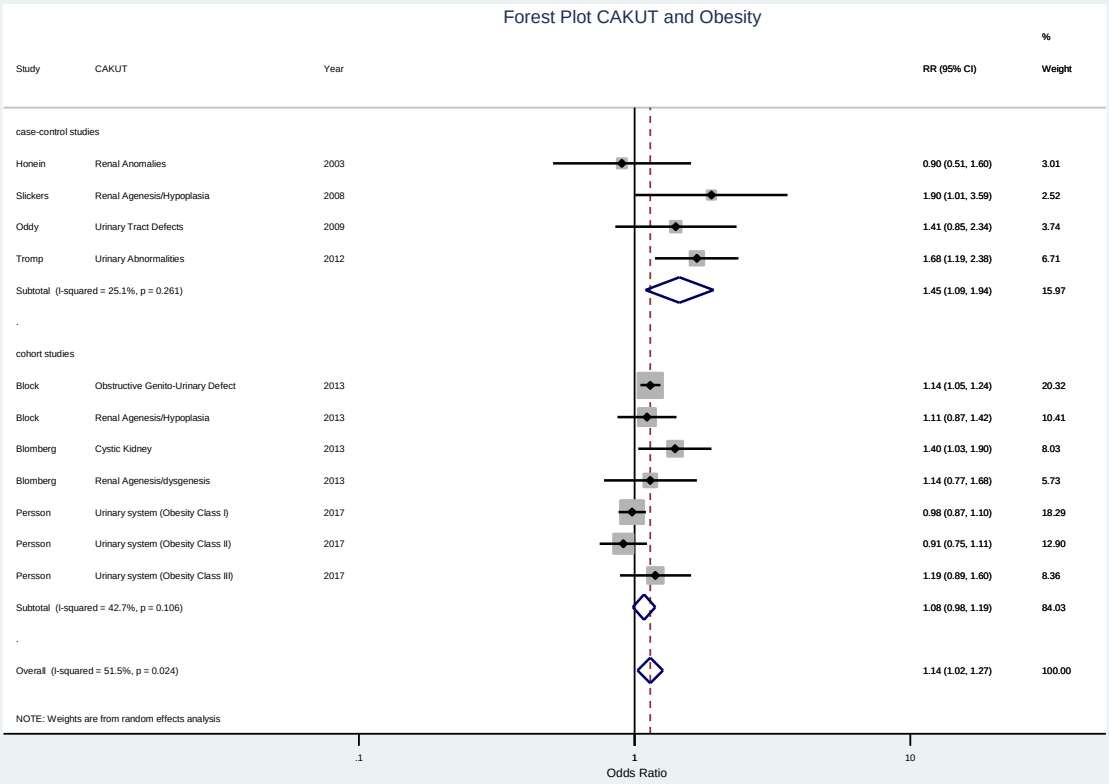

Figure 3: Prevalence of Obesity in Females aged 18 years or older 1980-2016

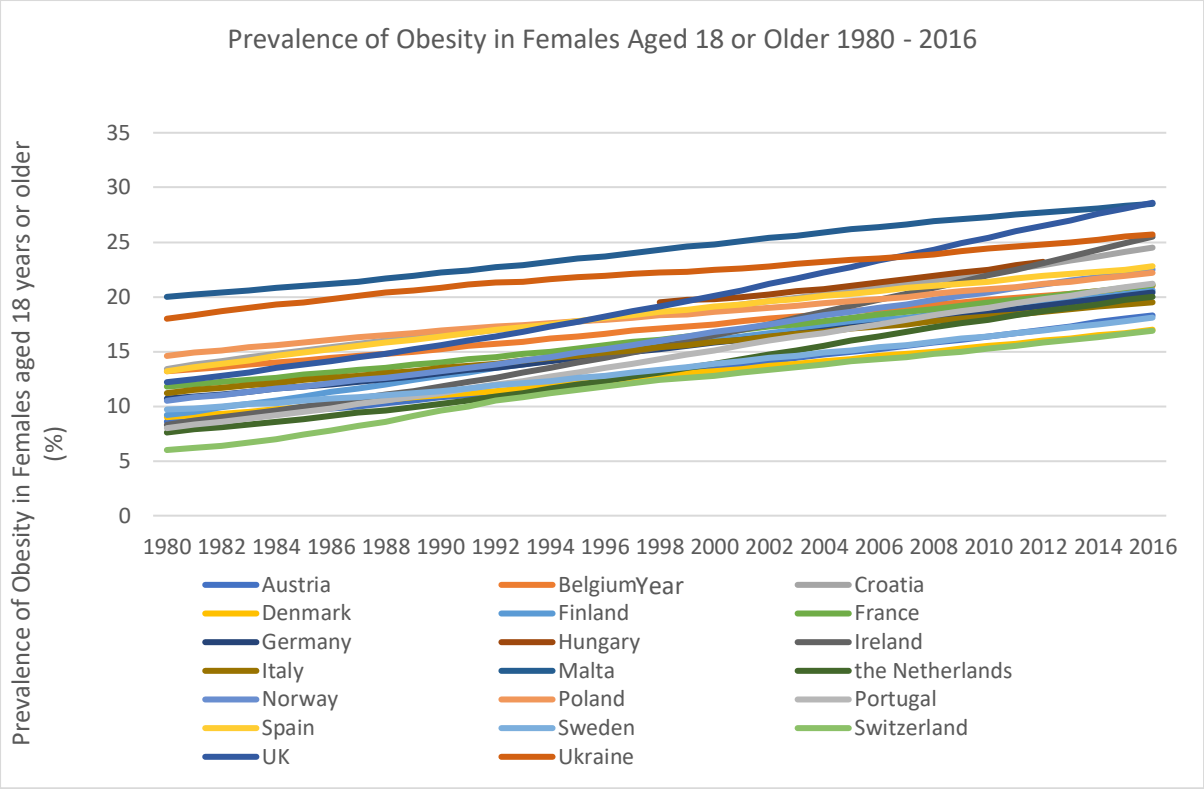

Figure 4: Incidence of CAKUT* in European countries 1980 to 2017 (anomalies included in CAKUT: congenital hydronephrosis, posterior urethral valves, prune-belly syndrome, multicystic kidney dysplasia and bilateral kidney agenesis)