EPIDEMIOLOGICAL ASPECTS OF CARDIOMETABOLIC RISK

Ph.D. Thesis

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List of papers included in the thesis

I. **Hulmán A**, Witte DR, Kerényi Zs, Tanczer T, Szabó E, Janicsek Zs, Madarász E, Tabák AG, Nyári TA. Heterogeneous effect of gestational weight gain on birthweight: quantile regression analysis from a population-based screening. (submitted to the *Annals of Epidemiology*)

II. **Hulmán A**, Tabák AG, Nyári TA, Vistisen D, Kivimaki M, Brunner EJ, Witte DR. Effect of secular trends on age-related trajectories of cardiovascular risk factors: the Whitehall II longitudinal study 1985-2009. *International Journal of Epidemiology* 2014; doi:10.1093/ije/dyt279.

III. **Hulmán A**, Færch K, Vistisen D, Karsai J, Nyári TA, Tabák AG, Brunner EJ, Kivimäki M, Witte DR. Effect of time of day and fasting duration on measures of glycaemia: analysis from the Whitehall II study. *Diabetologia* 2012;56:294-297.

1 INTRODUCTION

During the second half of the last century, the main focus of epidemiology turned from infectious to non-communicable disease (NCD). According to a WHO report, in 2008 the leading cause of death among NCD was cardiovascular disease (CVD) with 17 million cases, followed by cancer, chronic respiratory disease and diabetes. Beside premature deaths, morbidity that affects quality of life is also a major component of the burden of NCD. People with diabetes have a two- to fourfold risk of CVD and need approximately three times the health-care resources compared to those without diabetes.

Cardiometabolic risk is determined by various risk factors which play a key role in the pathophysiology which leads to CVD and type 2 diabetes. The four most important modifiable behavioural risk factors include tobacco smoking, sedentary lifestyle, unhealthy diet and excessive alcohol consumption. These lifestyle patterns result in adverse changes in metabolic risk factors, such as obesity, hypertension, hyperglycaemia and dyslipidemia.

Incidence rates for CVD dropped markedly in high-income countries and increased in low- and middle-income countries in the last few decades. Although blood pressure and cholesterol levels fell in high-income regions, the prevalence of obesity and diabetes increased markedly. Developing countries are experiencing the effects of globalisation and urbanisation similar to those previously seen in western populations, which calls for action to prevent a possibly huge burden of CVD. In-depth data collection and novel, sophisticated statistical analyses can help to understand the reasons of contrasting trends in risk factors and to evaluate the effect of potential prevention strategies.

The present thesis examines three different epidemiological aspects of cardiometabolic risk: the effect of maternal obesity and gestational weight gain (GWG) on birthweight; age-related trajectories and secular trends of risk factors; and diurnal variation of glucose measures and its consequences on diabetes diagnosis.

1.1 Maternal obesity and gestational weight gain (Study 1)

Maternal pre-pregnancy BMI and GWG are well-known determinants of infant birthweight, while both low and high birthweight contribute to the risk of adverse pregnancy outcomes and later health problems in offspring. GWG is associated with birthweight, independently from maternal BMI. This offers an opportunity to counterbalance the negative effects of too low or high pre-pregnancy BMI by optimizing GWG. Current recommendations from the Institute of Medicine (IOM) reflect the premise that a larger GWG is acceptable in underweight women to prevent small for gestational age (SGA) newborns, while only a limited weight gain is desirable in obese women to reduce the risk of large for gestational age (LGA) newborns. However, current knowledge and recommendations are based on ordinary least squares (OLS) and logistic regression models that lack detail about associations along entire distributions of the continuous outcome variable birthweight. This aspect is especially important when analysing determinants of birthweight, when both ends of the distribution increase the risk of adverse health outcomes. Therefore, a prevention strategy that decreases the variation and kurtosis of birthweight is preferable compared to a strategy that induces a left-shift of the entire birthweight distribution.

1.2 Secular trends and age-trajectories of risk factors (Study 2)

Our current knowledge on the age-related progression of cardiometabolic risk factors is often still based on cross-sectional analyses comparing mean values. Such studies cannot capture within-individual changes and might be strongly affected by cohort effects. The last few decades brought marked changes in cardiometabolic risk, which makes the analysis of age-related trajectories especially challenging. Changes of mean levels give only a limited description of secular trends, while changes in risk factor distributions still receive little attention. Most of the evidence is on BMI, suggesting that distributions have become increasingly right-skewed in the past decades, with little right shift of the entire curve. Nevertheless, distributions of other risk factors were rarely analysed simultaneously.

1.3 Diurnal variation of glucose measures (Study 3)

The consequences of a diabetes diagnosis are lifelong and therefore a diagnosis should be made carefully. Diurnal variation of glucose tolerance was described more than 40 years ago, nevertheless it is still not taken into account sufficiently in clinical practice and in epidemiological studies. Current recommendation regarding oral glucose tolerance tests (OGTT) are very permissive and previous evidence suggests that even if following them, measures can vary by time of day and fasting duration. Therefore we hypothetized that there may be remaining heterogeneity in the results of OGTTs even if they are performed according to the current instructions, and that the magnitude of this heterogeneity has the potential to affect the number of diabetes diagnoses in large epidemiological studies.

2 AIMS

- To characterise the effect of pre-pregnancy BMI and maximal GWG on the entire distribution of birthweight. We also wanted to compare how a hypothetical population-based and a high-risk intervention strategy promoting a more modest GWG would perform in the prevention of low birthweight and macrosomia.

- To investigate how secular trends affected cardiometabolic risk factor distributions (e.g. location shift or changing skewness) in the last three decades by applying non-parametric statistical methods. We also aimed to examine age-related risk factor trajectories and how these were affected by secular trends.

- To explore the individual and the joint effect of time of day and fasting duration on FPG, 2hPG and HbA_{1c} and to assess whether these associations are affected by ageing and obesity. We also aimed to evaluate the effect of timing on the incidence of diabetes in a large occupational cohort study.

3 METHODS

3.1 Study 1

We analysed data from a population-based gestational diabetes mellitus (GDM) screening conducted at the Szent Imre Teaching Hospital between 2002 and 2005 in Budapest, Hungary. Altogether, 5,335 pregnancies were registered during the study period. After excluding twin pregnancies, stillbirths and records with missing birthweight values or other covariates, the final dataset included 4,925 cases (92% of all pregnancies). Data on covariates and outcomes were collected with questionnaires at the time of the OGTT between week 22 and 30 of gestation, immediately after delivery or were extracted from hospital records. Maternal age, ethnicity, education, smoking status, parity, pre-pregnancy weight, maximal GWG and treatment for GDM were recorded. Infants' birthweight and sex were extracted from hospital documentation.

We analysed the BMI-birthweight and the GWG-birthweight associations with multivariable quantile regression models. We investigated the modifying effect of BMI on the GWG-birthweight association by including the BMI×GWG interaction in the models. All analyses were adjusted for week of delivery, infant's sex, maternal education, ethnicity, age, height, smoking status, parity and intervention during pregnancy. Classical regression models were also fitted with exactly the same variables.

We estimated the effect of a hypothetical population-based (-2 kg GWG among all women) and a high-risk (-3 kg GWG among overweight and obese women) prevention strategy by utilising coefficient estimates from the quantile regression models. The proportion of low birthweight and

macrosomic infants, and the standard deviation (SD) of birthweight (a measure of dispersion of the outcome) were calculated from the new hypothetical birthweight distribution.

3.2 Study 2

We analysed data from the Whitehall II occupational cohort study. Between 1985 and 1988, 10,308 men and women, aged 35-55 years and employed in London-based government departments, participated in the first phase of the study. Clinical examinations in addition to postal questionnaires were part of every second phase. This resulted in up to five repeated measurements per individuals during the 25 years of follow-up.

Secular trends of risk factors were investigated in a subgroup of participants aged 57-61 stratified by sex. This age group was not represented at phase 1, when participants were at 35-55 years of age, so the study period for this analysis was 18-year long (1991-2009). We first described changes in body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol by calculating the 10th, 50th and 90th percentiles at each phase. Linear trends were estimated for these specific percentiles with quantile regression models. Smooth kernel distributions were fitted to the data to get an overall picture of distributional changes.

Quadratic age-related risk factor trajectories for the mean were assessed by fitting mixed-effects models with random intercepts for the entire Whitehall II cohort, stratified by sex. Year of birth and its interaction terms with age and age-squared were included in the models to investigate secular trends and cohort effects. Using these model terms, we could account for possible differences in trajectory characteristics (level and curvature) between birth cohorts. Sensitivity analyses were conducted to test the robustness of our results against selective loss of follow-up and healthy survival.

3.3 Study 3

We analysed data from the Whitehall II study, which was previously described. FPG and 2hPG measures were assessed with a 75-g OGTT with glucose measurements at 0 and 120 minutes (starting times between 08:00 and 15:00 hours) that was part of the clinical examination from phase 3 onward. HbA_{1c} was measured in phases 7 and 9. Blood samples were handled according to standard protocols. Time of fasting blood draw was recorded as HH:MM on the participant's clinical report form. Fasting duration was calculated from the time of the last meal, which was self-reported. Participants with diabetes and missing anthropometric measures were excluded from the analyses. The final dataset included 5,978 participants (with 13,269 person-examinations) of white ethnicity.

The effect of time of day and fasting duration on glucose measures (FPG, 2hPG and HbA_{1c}) was assessed with age- and BMI-adjusted mixed-effects models that were stratified by sex. Models with 2hPG as outcome variable included further adjustment for height. All models were adjusted for study phase (included as a categorical variable) to model potential phase-specific, systematic differences in measurements. To handle the within-person correlation arising from the longitudinal structure of the data, random effects for the intercept were included in the models. We also fitted all models with standardised outcomes to investigate the relative effect of timing factors on glucose measures. After the individual effect of time of day and fasting duration had been examined, all models were fitted with both variables at the same time. The effect of ageing and BMI on diurnal variation was analysed by including the appropriate interaction terms in the models.

4 RESULTS

4.1 Study 1

Participants were relatively lean with a mean BMI of 22.7 ± 4.1 kg/m^2 and low prevalence of overweight (15%) and obesity (6%). They were

predominantly Caucasian (98%) and abstained from smoking during pregnancy (95%). Almost 90% of participants finished at least high school. Maternal GWG and pre-pregnancy BMI were both positively associated with birthweight (in a mutually adjusted model). Effect sizes increased towards higher percentiles of the birthweight distribution, especially for pre-pregnancy BMI. Classical regression models described the association well only in the middle region of the birthweight distribution. The effect of GWG on birthweight was modified by pre-pregnancy BMI. At a pre-pregnancy BMI of 20 kg/m^2, a 1 kg difference in GWG was associated with a 10.2 [95% CI: 6.1; 14.5] g and 23.1 [17.5; 29.0] g higher birthweight at the 5th and 95th percentile of birthweight, respectively. In contrast, at a pre-pregnancy BMI of 30 kg/m^2, we did not observe an increasing trend by quantile in effect sizes, which ranged from 18.6 to 26.0 g along the birthweight distribution.

The relative decrease in the proportion of macrosomic infants (-15%) was greater than the increase in low birthweight (+12%) after a hypothetical population-based prevention strategy. Using coefficient estimates from classical regression models resulted the opposite (-13% and +17%, respectively). The high-risk strategy slightly increased the proportion of low birthweight infants, but the presence of macrosomia decreased only by 6%.

4.2 Study 2

Distributional changes of risk factors were strong in the 57-61 age group. Changes in the BMI distribution of men were characterised by a right-shift of the median and a fattening right tail. Increments were heterogeneous along the distribution and were the largest at the 90th percentile (+2.8 kg/m^2). For women the low BMI segment remained unchanged, but the 90th percentile increased by 2 kg/m^2. WC increased along the entire distribution. The increment was largest at the right end of the distribution (+8 cm at the 90th percentile) in both men and women. The change in SBP was not consistent: it increased until phase 7 and then dropped markedly at phase 9. Therefore the linear trend cannot be interpreted. In contrast the entire DBP distribution shifted to the left by

approximately 10 mmHg in both men and women. The linear trend was of similar magnitude along the entire TC distribution, which led to a left-shift of the distribution with 1.5 mmol/l in both men and women. Changes in HDL cholesterol were modest compared to TC, although all percentiles increased by 0.1-0.2 mmol/l.

Trajectories of BMI and WC increased faster with age and were at higher levels at any given age in younger birth cohorts than in older. The BMI difference between those born in 1933 and 1948 at age 60 was 1.3 [1.1; 1.5] kg/m^2 and 0.5 [0.1; 0.9] kg/m^2 in men and women, respectively. The increasing trend of BMI was more marked in men, while women had steeper BMI and WC trajectories in mid-life. SBP increased faster between ages 40 and 75 in women than in men: 15.1 mmHg versus 8.9 mmHg, which was a 12.9% and 7.2% relative increase, respectively. Younger generations had generally lower mean SBP, except elderly men. The unadjusted mean DBP trajectory had its peak around age 50 and then declined markedly. In the adjusted models, younger generations' trajectories started to decline earlier and had lower DBP at any age. The unadjusted TC trajectory of men increased up to age 47, peaking at 6.2 [6.2; 6.3] mmol/l. In women, the peak occurred slightly later at age 52, when the peak value was 6.3 [6.3; 6.4] mmol/l. At age 60, men born in 1948 had 1.1 [1.0; 1.2] mmol/l lower TC level than men born in 1933, whereas for women the difference between these birth cohorts was 1.2 [1.1; 1.3] mmol/l. Women had a higher mean HDL cholesterol level than men. We observed a modest increase with both age and calendar year. We found similar associations in our sensitivity analyses).

4.3 Study 3

OGTTs were performed between 08:00 and 15:00 (median 10:42, Q1-Q3: 9:50-11:36), whereas fasting duration ranged from 8 to 20 hours (median 13.4, Q1-Q3: 12.1-14.9). Time of day and fasting duration were moderately correlated (Pearson r = 0.6, p<0.001). FPG was inversely associated with both time of day and fasting duration. The mean difference in FPG between measures at 08:00 and 15:00 was -0.46 [-0.50; -0.42]

mmol/l in men and -0.39 [-0.46; -0.31] mmol/l in women. The effect of fasting duration was markedly attenuated after including both predictors in the model. Time of day and fasting duration were positively associated with 2hPG. The mean difference between measures at 08:00 and 15:00 was 1.39 [1.25; 1.52] mmol/l in men and 1.19 [0.96; 1.42] mmol/l in women. Time of day and fasting duration were independently associated with 2hPG even after the inclusion of both variables in the model. HbA_{1c} levels were neither associated with time of day nor with fasting duration. Models with standardised outcome variables showed that the relative impact of time of day and fasting duration on FPG and 2hPG were similar of magnitude, but in the opposite. A higher BMI, but not increased age was associated with larger diurnal variation in FPG. We observed the opposite relationship for 2hPG: diurnal variation increased with ageing, but not with BMI. We modelled the hypothetical situation that all OGTTs started at 09:00 to investigate the effect of our findings on the diagnosis of diabetes in a clinical setting. In this scenario, we found that 15% of people with WHO-defined diabetes would have not received a diabetes diagnosis. The number of people with "newly" diagnosed diabetes was not clinically relevant.

5 DISCUSSION

5.1 Study 1

Geoffrey Rose's population strategy still shapes public health practice and preventive medicine. Classical regression models focusing on mean values cannot model distributional changes in an outcome variable, because that would assume homogeneity in associations along the entire outcome distribution. Our results showing varying effect sizes of BMI and GWG makes clear that the assumption of homogeneity does not hold for the BMI-birthweight and the GWG-birthweight association. Use of classical regression may result in an underestimation of the expected decrease in macrosomia and an overestimation of the increase in low birthweight for a given population-wide reduction in GWG. Such results may lead to false conclusions and even decisions on prevention policies. Our analyses suggest

that quantile regression is a more suitable tool to describe complex associations than classical regression. The population-based approach (-2 kg GWG in all individuals) led to decreased dispersion (measured by SD) of the birthweight distribution, which is favourable from a public health perspective. This is the opposite of the common criticism that Rose's population approach increase inequalities.

The population approach is usually set against a population-at-risk strategy that targets only individuals at high risk. Such a strategy can be successful if accurate risk assessment tools are available. Unfortunately, the prediction of fetal macrosomia is a difficult task, because of complex associations of environmental and genetic factors that determine fetal growth. Our hypothetical high-risk strategy underperformed the population approach in the prevention of macrosomia. This was due to a relatively high proportion of macrosomic infants, who were born to normal weight women. Our study population was relatively lean: 21% of participants were overweight or obese. The increase in low birthweight following the high-risk strategy was negligible.

The heterogeneous effect of BMI and GWG on birthweight offers an opportunity to diminish the right tail of the birthweight distribution without increasing the number of low birthweight infants. Our results showed that a population approach promoting a more modest GWG in all women may offer greater benefits on a population-level, than a high-risk approach in a relatively lean population. This notion highlights the clinical and public health importance of our findings and show how quantile regression may help to define risk reduction strategies in the presence of complex associations between risk factors and outcomes.

5.2 Study 2

General obesity trends are usually described by reporting mean BMI levels. These results are easily interpreted, but give no information about the shape of distributions. Another usual approach is to report the prevalence of overweight and obesity. This gives more, but still limited information on the

higher segment of the BMI distribution. Studies focusing on entire distributions showed an increased right-skewness. The increasing BMI trend was more marked in men. This finding strengthens previous evidence showing that obesity levels in men are catching up with women. One explanation might be a sex difference in the attitude to weight management. We observed that while BMI did not increase in leaner groups, they still developed abdominal obesity indicated by a right-shift of the WC distribution's lower segments. A possible explanation is that people lose muscle mass and simultaneously accumulate abdominal fat mass, because of more sedentary lifestyles. This notion is even more concerning in light of previous results showing a strong association between abdominal obesity and glucose metabolism independently from general obesity. Our longitudinal trajectory analyses showed that younger generations experience a greater cumulative exposure to obesity. Participants born only 15 years later (in 1948 versus 1933), reached overweight 10 and 6 years earlier in their life-course in men and women, respectively. This notion suggests that younger birth cohorts might be at a greater cardiometabolic risk and that prevention of obesity is of major importance already at an early age in the life-course.

Contrary to our observations in obesity measures, distributional trends in SBP were not consistent in one direction between phases. A marked decline was observed only between phase 7 and 9, especially in women. We cannot fully attribute this to a wider use of antihypertensive medication, because that increased already between earlier phases. In contrast, both our sequential cross-sectional and longitudinal analyses confirm a marked decline in DBP. The drop was similar along the entire distribution, which resulted a left-shift of the distribution. Regarding the age-related blood pressure trajectories, our results are in line with current understanding that SBP rises from mid to late adulthood (more rapidly among women), while DBP peaks around the age of 50 years and then starts to decline, because of increasing aortic and small vessel stiffness. Compared to previous studies, our analyses accounted for secular trends and cohort effects that made it possible to observe different trajectory characteristics between birth cohorts.

In addition to generally lower DBP levels, we also found that the decline started at a lower age in younger birth cohorts. As DBP is inversely associated with the risk of coronary heart disease after age 60, this notion imposes additional risk on younger birth cohorts. The decreasing trends in SBP and especially in DBP have to be interpreted with caution. As DBP decreases with age while SBP increases, a widening gap develops between SBP and DBP that leads to an increasing pulse pressure, which is an independent determinant of the coronary heart disease.

Our results showed a marked left-shift of the entire TC distribution. Although the observed decline may be partially due to the wider use of statins, especially in elderly, this cannot be the only cause, as values decreased in the left tail of the distribution too. This finding is in line with previous reports from developed countries emphasising the importance of positive changes in dietary patterns. Our analyses showed that the age-related trajectories of younger cohorts started to decline at younger ages in the life-course. It is likely because of decreasing thresholds above which lipid-lowering treatment is prescribed. The effect of secular trends and cohort effects were so large during the last three decades that an unadjusted TC trajectory clearly underestimates true trajectories in late adulthood. This effect makes it a challenging task to isolate the effect of ageing from trends. Trends in HDL cholesterol are rarely investigated. Both of our models suggest favourable changes in HDL cholesterol levels in the last three decades. Although changes were modest compared to TC.

5.3 Study 3

The observed decline in FPG levels during the day is in line with previous findings, which also showed clinically relevant differences between morning and early afternoon FPG measures. Our findings support the notion that standardisation of fasting duration and time of day is an important point in the protocols of epidemiological studies. Glucose measures even from fasting subjects are not necessarily unbiased, so adjustment for timing factors is advisable if data are available. These results indicate that timing should not be ignored when diagnosing diabetes, or

comparing individual glucose levels longitudinally in clinical practice. Our results are also consistent with previous findings on the modest role of fasting duration in addition to time of day.

Our results show increasing 2hPG levels during the day. We also confirmed the notion that diurnal variation in glucose tolerance increases with age. However, we found no clear evidence to suggest that obesity would reduce diurnal variation in 2hPG. Fasting duration improved our models for 2hPG even if time of day was accounted for. Although the studies are not directly comparable, our results support the recent finding of an underestimation of glucose tolerance among pregnant women who had an afternoon rather than a morning 1-hour, 50 g, non-fasting glucose challenge test, as compared to a confirmatory morning 3-hour, 100 g fasting OGTT performed on a separate day. HbA_{1c} measures were independent of both time of day and fasting duration.

6 CONCLUSIONS

6.1 Maternal obesity and gestational weight gain

- We demonstrated the rarely exploited potential of quantile regression in public health and preventive medicine.
- The association between gestational weight gain and birthweight was altered by BMI and was heterogeneous in leaner women.
- Based on a statistical model, we found that a population-based intervention promoting a more modest gestational weight gain might offer more favourable changes in the birthweight distribution, than a high-risk approach.

6.2 Secular trends and age-related trajectories of risk factors

- Trends of cardiometabolic risk factors were described using sophisticated statistical methods focusing on entire distribution characteristics and not only on mean levels.
- The obesity epidemic affected those already overweight and obese, which led to increasing dispersion and right-skewness of distributions.
- The marked drop in diastolic blood pressure has to be interpreted with caution, because of its negative effects in elderly and the increasing pulse pressure.
- Secular trends were strong and heterogeneous in the last decades and therefore should be taken into account when analysing age-related trajectories to avoid biased estimates caused by large differences between successive birth cohorts.

6.3 Diurnal variation of glucose measures

- We investigated the combined effect of time of day and fasting duration on all three glucose measures, based on a large sample.
- We gave estimates for the magnitude of diurnal variation by keeping time of day and fasting duration as continuous variables.
- Time of blood sampling and fasting duration have clinically relevant effects on glucose measures even if WHO recommendations are followed.

ÖSSZEFOGLALÓ

Az elmúlt évszázad második felében az epidemiológia vizsgálatok középpontjába a nem-fertőző megbetegedések kerültek. Egy 2010-es WHO jelentés szerint a legtöbb nem-fertőző megbetegedés miatti halálozás oka kardiovaszkuláris megbetegedés volt (17 millió eset világszerte 2008-ban). Korunk egyik népbetegsége a 2-es típusú cukorbetegség (kb. 10%-os prevalencia a 25 év feletti lakosság körében), mely szoros összefüggésben áll napjaink egyik legsúlyosabb népegészségügyi problémája, az elhízással. A kardiovaszkuláris megbetegedések kockázata 2-4-szeres a cukorbetegek körében. Egy egyén kardiometabolikus kockázatát olyan rizikótényezők határozzák meg, melyek szerepet játszanak a kardiovaszkuláris megbetegedések és a 2-es típusú cukorbetegség kialakulásában. A tézisben három vizsgálatunkat mutatjuk be, melyek a kardiovaszkuláris kockázat különböző epidemiológia aspektusaival foglalkoznak:

- az elhízás és a terhesség alatti testsúlygyarapodás hatása az újszülöttek születési súlyeloszlására,
- kardiometabolikus rizikófaktorok szekuláris trendjei és életkor szerinti változása (testtömegindex, derékkörfogat, szisztolés és diasztolés vérnyomás, teljes és HDL koleszterin),
- vércukorértékek napközbeni változékonysága és ennek hatása a cukorbetegség diagnózisára.

Elhízás és terhesség alatti testsúlygyarapodás

A terhesség előtti elhízás és a terhesség alatti testsúlygyarapodás meghatározó tényezői a születési súlynak és a terhesség egyéb kimeneteleinek. Vizsgálatainkban a budapesti Szent Imre Kórházban 2002 és 2005 között zajló gesztációs diabétesz szűrőprogramból származó adatokat használtuk (>5000 terhesség). A terhesség alatti testsúlygyarapodás pozitív összefüggésben áll a születési súllyal, azonban kvantilis regresszió segítségével megmutattuk, hogy a hatás nagysága

vékonyabb nők esetén nem egyenletes az születési súlyok eloszlása mentén, hanem növekszik a magasabb percentilisek felé. Klasszikus lineáris regresszióval nem kaphatunk teljes képet ilyen komplex összefüggésekről, melyeknek fontos népegészségtani következményei vannak. Tanulmányunkban prevenciós stratégiák születési súlyok eloszlására vonatkozó hatását vizsgáltuk a regressziós együtthatók felhasználásával. Eredményeink azt mutatták, hogy a terhesség alatti testsúlygyarapodás populációs szintű csökkenése nem a születési súlyeloszlás egyenletes eltolódásához vezetne, hanem az eloszlás jobb végét befolyásolná nagyobb mértékben, valamint a változó varianciája is csökkenne. Kedvezőbb eredményeket kaptunk, mint egy intenzívebb, de csak túlsúlyos és elhízott nőket érintő stratégia esetén. Ez alapján azt sejthetjük, hogy a testsúlygyarapodásra vonatkozó ajánlások túlságosan megengedőek. Azt is kijelenthetjük, hogy a kvantilis regresszió kedvező tulajdonságai jelenleg nincsenek kihasználva epidemiológiai vizsgálatokban.

Kardiometabolikus rizikófaktorok: trendek és életkor szerinti változás

Az elmúlt 25 évben a kardiometabolikus rizikófaktorok eloszlásaiban jelentős változások történtek. Vizsgálatunkban több mint 10 000 fő, 25 éves követésből származó adatait elemeztük (Whitehall II vizsgálat, 1985-2009). Eredményeink azt mutatták, hogy a fiatalabb generációk bármely életkorban elhízottabbak voltak, mint korábban született társaik. Ezzel szemben, vérnyomás és koleszterin értékeik csökkentek az évek során. Az erős trendek a rizikófaktorok eloszlásainak alakját is nagyban befolyásolták. Amíg a testtömegindex és a derékkörfogat eloszlása jobbra-ferde lett, a teljes koleszterin és érdekes módon a diasztolés vérnyomás eloszlások teljes egészében balra tolódtak. A kardiovaszkuláris megbetegedések miatti halálozások számának csökkenése azt jelzi, hogy az elhízás növekvő mértékét ellensúlyozni tudták a vérnyomást és a koleszterinszintet meghatározó kedvező trendek. Ezenkívül valószínűsíthető, hogy a kardiometabolikus kockázatot meghatározó rizikófaktorok relatív fontossága és egymás közötti viszonya is változik. Ebből a megfigyelésből következik a különböző rizikókalkulátorok időről időre történő

újrakalibrálásának fontossága. Eredményeink arra is rámutattak, hogy populációs átlagok vizsgálata nem kielégítő és teljes eloszlásokat szükséges tekintenünk epidemiológiai vizsgálatokban. A különböző rizikófaktorok életkor szerinti változásának elemzésekor a szekuláris trendeket és kohorsz hatásokat nem szabad figyelmen kívül hagyni. Az ehhez szükséges statisztikai módszerek napjainkban már elérhetők a legtöbb statisztikai szoftverben.

Vércukorértékek napközbeni változékonysága

A cukorbetegség diagnózisa vércukorszint értékeken alapul, ezért a méréseket befolyásoló tényezők epidemiológiai vizsgálata kiemelten fontos feladat. Egy nagy számú mintán (Whitehall II, >10 000) megmutattuk hogyan befolyásolja a vérvétel ideje és az utolsó étkezéstől eltelt idő az éhomi és a 2-órás vércukorszintet, valamint a HbA_{1c} értéket. A nap előrehaladtával és az utolsó étkezés óta eltelt idő növekedésével az éhomi vércukor csökkent, míg a 2-órás vércukor nőtt. A HbA_{1c} értéket egyik tényező sem befolyásolta. Ezenkívül megmutattuk milyen hatással van a testtömegindex és az életkor ezekre az összefüggésekre. Eredményeink a cukorbetegség diagnosztizálásához használt glükóz tolerancia teszt standardizálására hívják fel a figyelmet a két vizsgált tényező szempontjából, melyek szerepe gyakran alábecsült a klinikai gyakorlatban és epidemiológiai vizsgálatokban. Az éhomi és a 2-órás vércukorszint értékek a jelenleg ajánlott 8 órás éhezés után is változtak, a mérés idejétől függetlenül. Ezen ingadozások befolyásolhatják az egyszeri mért érték alapján megállapított cukorbetegek számát epidemiológiai vizsgálatokban, még a WHO ajánlások betartása mellett is.