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*Original Research Paper*

## Glatiramer acetate during early pregnancy: A prospective cohort study

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### *Abstract*

**Background:** Only limited data are available on whether glatiramer acetate exposure during pregnancy has an effect on perinatal outcome.

**Objective:** To determine the effect of glatiramer acetate exposure during pregnancy on pregnancy outcomes in women with multiple sclerosis.

**Methods:** We compared the outcome of pregnancies of women with multiple sclerosis exposed to glatiramer acetate with pregnancies unexposed to disease-modifying therapies. Women were enrolled into the German Multiple Sclerosis and Pregnancy registry. A standardized questionnaire was administered during pregnancy and postpartum. Detailed information on course of multiple sclerosis and pregnancy, concomitant medications, labor, delivery, and outcome of pregnancy was obtained.

**Results:** We collected data on 246 multiple sclerosis pregnancies, 151 exposed to glatiramer acetate and 95 unexposed to disease-modifying therapies during pregnancy. Three (2.2%) congenital anomalies occurred in the exposed and 6 (6.7%) in the control group. We did not observe an increase in other adverse pregnancy or delivery outcomes including spontaneous abortions, preterm birth, Cesarean sections, or reduced birth weight in the exposed group.

**Conclusion:** Our data provide further evidence that glatiramer acetate exposure during the first trimester of pregnancy appears safe and without teratogenic effect. These findings provide important additive knowledge to better counsel women with multiple sclerosis in planning a pregnancy.

**Keywords:** Multiple sclerosis, pregnancy, disease-modifying therapies, glatiramer acetate, safety, pregnancy outcomes

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### **Introduction**

Many patients with multiple sclerosis (MS) start early in the course of the disease with various disease-modifying therapies (DMTs), as early relapse prevention is thought to have favorable effect on the course of the

pregnancies from eight studies and found no safety signals on the outcome of pregnancy, labor, or delivery. The authors considered the results as not compelling due to small sample size.<sup>5</sup> Teva Pharma, the GLAT manufacturing company, had never published their post-marketing pregnancies in a scientific manu-

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RESEARCH ARTICLE

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## Evidence for the free radical/oxidative stress theory of ageing from the CHANCES consortium: a meta-analysis of individual participant data

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### Abstract

**Background:** The free radical/oxidative stress theory of ageing has received considerable attention, but the evidence on the association of oxidative stress markers with mortality is sparse.

**Methods:** We measured derivatives of reactive oxygen metabolite (D-ROM) levels as a proxy for the reactive oxygen species concentration and total thiol levels (TTL) as a proxy for the redox control status in 10,622 men and women (age range, 45–85 years), from population-based cohorts from Germany, Poland, Czech Republic, and Lithuania, of whom 1,702 died during follow-up.

**Results:** Both oxidative stress markers were significantly associated with all-cause mortality independently from established risk factors (including inflammation) and from each other in all cohorts. Regarding cause-specific mortality, compared to low D-ROM levels ( $\leq 340$  Carr U), very high D-ROM levels ( $> 500$  Carr U) were strongly associated with both cardiovascular (relative risk (RR), 5.09; 95 % CI, 2.67–9.69) and cancer mortality (RR, 4.34; 95 % CI, 2.31–8.16). TTL was only associated with CVD mortality (RR, 1.30; 95 % CI, 1.15–1.48, for one-standard-deviation-decrease). The strength of the association of TTL with CVD mortality increased with age of the participants (RR for one-standard-deviation-decrease in those aged 70–85 years was 1.65; 95 % CI, 1.22–2.24).

**Conclusions:** In these four population-based cohort studies from Central and Eastern Europe, the oxidative stress serum markers D-ROM and TTL were independently and strongly associated with all-cause and CVD mortality. In addition, D-ROM levels were also strongly associated with cancer mortality. This study provides epidemiological evidence supporting the free radical/oxidative stress theory of ageing and suggests that d-ROMs and TTL are useful oxidative stress markers associated with premature mortality.

**Keywords:** Cancer mortality; Cardiovascular mortality; Cohort study; Death; Epidemiology; Free radicals; Meta-analysis



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ORIGINAL CONTRIBUTION

## Relative validation of 24-h urinary hippuric acid excretion as a biomarker for dietary flavonoid intake from fruit and vegetables in healthy adolescents

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### Abstract

**Purpose** A biomarker for dietary flavonoid intake from fruit and vegetables (FlavFV) is needed to elucidate the relevance of flavonoids from these sources for the prevention of chronic diseases. Urinary hippuric acid (HA)—a major metabolite of flavonoids—is promising in this respect as it was shown to satisfyingly indicate fruit and vegetable consumption in different age groups. Therefore, we validated urinary HA as a biomarker for intake of FlavFV.

**Methods** Analyses included data from 287 healthy adolescents of the DONALD Study (aged 9–16 years) for whom a minimum of two pairs of HA measurements from 24-h urine samples (test method) and FlavFV intake estimated from 3-day weighed dietary records (reference method) existed. Agreement between both methods was assessed by Spearman correlation and cross-classification analyses. Possible confounders of the association were identified by linear regression models. Analyses were performed using a

into opposite quartiles. These findings were corroborated by analyses in the confirmatory sample ( $r_{\text{unadjusted}} = 0.64$ ; 88 % in same/adjacent vs. 4 % in opposite quartiles). Body surface area (BSA) was the only relevant covariate in the exploratory sample, and its adjustment improved cross-classification estimates in both subsamples.

**Conclusions** BSA-adjusted 24-h urinary HA excretion represents a suitable biomarker of habitual FlavFV intake in healthy adolescents.

**Keywords** 24-h Urine · Adolescents · Biomarker of intake · Flavonoids · Hippuric acid · Relative validation

### Introduction

Beneficial effects of high fruit and vegetable (FV) intake on chronic disease development are thought to be partly attrib-