The METEOR study of diabetes and other metabolic disorders in patients with schizophrenia treated with antipsychotic drugs. I. Methodology

MARC DE HERT,¹ MAURO MAURI,² KEN SHAW,³ TILMAN WETTERLING,⁴ ADAM DOBLE,⁵
AGNÈS GIUDICELLI⁶ & BRUNO FALISSARD⁷

1 UPC KUL Campus Kortenberg, Kortenberg, Belgium

2 Clinica Psichiatrica, DPFNB, Università di Pisa, Pisa, Italy

3 Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust, Cosham, UK

4 Vivantes Klinikum Hellersdorf, Klinik für Psychiatrie und Psychotherapie – Gerontopsychiatrie, Berlin, Germany

5 Foxymed, Fresnes, France

6 Sanofi-aventis, Paris, France

7 INSERM U669, PSIGIAM, Maison de Solenn, Paris, France

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Correspondence

Marc De Hert, University
Psychiatric Centre, Catholic
University Leuven,
Leuvensesteenweg 517, 3070
Kortenberg, Belgium.
Telephone (+32) 2-758-05-11
Fax (+32) 2-759-98-78
Email:
marc.de.hert@uc-kortenberg.be

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Abstract

Patients with schizophrenia present a two- to three-fold higher prevalence of diabetes, of metabolic syndrome and of cardiovascular morbidity. The reason for this increased prevalence may involve intrinsic vulnerability, lifestyle factors and iatrogenic effects of antipsychotic drugs. The objective of this multinational, cross-sectional, pharmacoepidemiological study was to determine the prevalence of diabetes, lipid disorders, obesity, hypertension and the metabolic syndrome in patients with schizophrenia treated with antipsychotic drugs. Particular attention was taken to acquire data on a wide range as possible of demographic, clinical and lifestyle variables that may influence the risk of metabolic disorders, which were taken into account in the calculation of prevalence data by propensity scoring. The study included 2270 subjects from 16 European countries, predominantly from Central and Eastern Europe. The proportion of subjects presenting the pathologies of interest was relatively high, ranging from 28% for glycaemic disorders to 70% for lipid disorders. Copyright © 2010 John Wiley & Sons, Ltd.

Introduction

An association between schizophrenia and an increased risk for type 2 diabetes mellitus has been considered for

nearly a century (Henderson, 2005). Studies performed in Italy (Mukherjee *et al.*, 1996), France (Casadebaig *et al.*, 1997), United States (Dixon *et al.*, 2000; Lamberti *et al.*, 2004) and, most recently, Belgium (De Hert *et al.*, 2006)

have indicated that the prevalence of type 2 diabetes in patients with schizophrenia may be up to 15%, twice as high as in the general population, and up to five times as high as in age-matched controls. In particular, type 2 diabetes appears to affect younger individuals with schizophrenia than it does in the general population. The interpretation of these findings is unclear, and may reflect contributions from lifestyle risk factors (for example, patients with schizophrenia are often sedentary and overweight), barriers to access to health care, a risk associated with the underlying pathophysiology of schizophrenia and an effect of antipsychotic drug treatments. Indeed, many studies have implicated an iatrogenic effect of certain antipsychotic drugs in the development of metabolic anomalies in patients with schizophrenia (Newcomer, 2005; Scheen and De Hert, 2007; Smith *et al.*, 2008; Tschoner *et al.*, 2007). Unravelling these different factors is a major public health issue and has important consequences for management of these patients to prevent the emergence of type 2 diabetes. More recently, prevalence rates of diabetes, hypertension and lipid disorders were evaluated systematically and prospectively in a large cohort of 1460 patients with schizophrenia entering a randomised, observational comparative study of antipsychotic treatment in the United States (CATIE study) (Nasrallah *et al.*, 2006). In this study, the prevalence of diabetes and treatment rates were not notably different from those reported in the general population of the United States, although the study population was considerably younger. When the study population was compared to a control sample matched for demographic variables, a four-fold higher prevalence of diabetes was observed in the CATIE patients compared to the control sample (Goff *et al.*, 2005).

An apparently elevated risk of diabetes is not the only such risk observed in patients with schizophrenia; morbidity and mortality from cardiovascular disease are generally high (Brown *et al.*, 2000; Fleischhacker *et al.*, 2008; Osby *et al.*, 2000). The prevalence of the metabolic syndrome and other cardiovascular risk factors is considerably higher in patients with schizophrenia. A recent review suggested that the relative risk of obesity, smoking, hypertension, dyslipidaemia and the metabolic syndrome, as well as of diabetes, compared to the general population ranged from 1.5 to 5 (Correll, 2007). Indeed, over 30 studies have now provided consistent evidence for a two- to three-fold higher prevalence of the metabolic syndrome in patients with schizophrenia, regardless of ethnic group and health care context (De Hert *et al.*, 2009).

There are, however, a number of limitations to the available risk assessments. For example, most of the available data come from retrospective analyses, are often limited by

the lack of appropriate case controls, of inadequate case ascertainment and of incomplete information on other potential risk factors. In particular, information on lifestyle factors such as smoking status, alcohol and substance use, food intake behaviour or physical activity is rarely available. It should also be noted that the majority of the data on antipsychotic use, schizophrenia and metabolic disorders has been generated on the North American subcontinent, where the distribution of lifestyle risk factors, the organisation of the health care system and antipsychotic prescription practices differ from those observed in Europe.

For this reason, we have undertaken a large, prospective, multinational pharmacoepidemiological study of diabetes and other metabolic disorders in patients with schizophrenia receiving antipsychotic drugs in Europe, the *Evaluation of metabolic disorders in schizophrenic patients* (METEOR) study. The primary objective of this study was to provide an estimate of the prevalence of metabolic disorders in patients with schizophrenia treated with antipsychotic drugs in different European countries. Secondary objectives were to identify risk factors for metabolic disorders in these patients, with a particular focus on the type of antipsychotic drug treatment that they received.

The study presented a number of specific methodological challenges. Firstly, it was necessary to generate a large, representative sample of patients with schizophrenia in participating European countries, including several in Eastern Europe where representative panels of physicians and patients for use in epidemiological surveys have not generally been established. Secondly, we needed to ensure that the diagnosis of schizophrenia and the data on metabolic variables were ascertained by the participating physician, and that information on a wide range of potential risk factors as possible was collected in a systematic fashion. In order to separate the effects of potential confounding risk factors from those of antipsychotic drug treatment, an appropriate powerful statistical method was required.

This article describes the methodology of the study and a description of the population included. Data on prevalence of the various metabolic disorders of interest and on associations between antipsychotic drug treatment and metabolic disorders will be reported elsewhere.

Subjects and methods

Study design

This multicentre, cross-sectional pharmacoepidemiological study was performed by 182 hospital-based or community psychiatrists in 12 European countries (Bulgaria,

Czech Republic, Estonia, Germany, Greece, Italy, Latvia, Lithuania, Romania, Russia, Slovenia and Turkey) between November 2006 and August 2007. In each country, physicians invited to participate were chosen to reflect local psychiatric practice and the patient management care of each country and to be representative of the regional diversity of the country. To this end, a local representative of the study sponsor provided a breakdown of psychiatric health care provision by sector for each country (for example, private *versus* public, hospital *versus* community) and centres were selected to match this breakdown. Capacity to recruit the required number of patients and to comply with protocol requirements for blood sampling were also taken into consideration. In certain countries, a coordinating investigator was designated by the study sponsor to recruit centres invited to participate. Local investigator meetings could be held before initiating patient recruitment, although this was not a protocol-stipulated requirement of the study. No limit was put on the number of participating investigators in each country. Each investigator included subjects during a six-month recruitment period.

Subjects

The study included subjects aged 18 years and older with all subtypes of schizophrenia, including schizophreniform and schizoaffective disorders according to the American Psychiatry Association Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV) diagnostic criteria (DSM-IV class 295.XX) (American Psychiatric Association, 2000). Subjects were required to be stabilised and treated with an antipsychotic drug for at least three months. Subjects presenting with an acute episode of schizophrenia, presenting with an acute non-psychiatric condition or emergency event or subjects participating in a clinical trial were excluded from the study.

Screening log and inclusion

In order to ensure that the planned number of subjects were included in each country, and to allow stratification according to type of antipsychotic medication, each participating physician maintained an anonymous online patient screening log. This was consolidated centrally by country on a weekly basis to ensure stratification until the assigned country quota was filled. For each subject, the screening log collected information on age, gender, presence of a diagnosis of schizophrenia, antipsychotic treatment [first- or second-generation antipsychotics (FGA or SGA)], whether the subject was included into the METEOR study, and, if not, why not (failure to match

the eligibility criteria, refusal to participate or other reason).

At each centre, between eight and 40 subjects were to be included. All subjects fulfilling the entry criteria consulting during the recruitment period were included sequentially in the study up to a maximum of 40. These were stratified according to treatment into either the FGA stratum or the SGA stratum in a ratio of one to three. This ratio was chosen since it corresponds to the relative weight of the two classes of antipsychotic drugs in current European prescription practice (IMS Health, 2006). For subjects prescribed multiple antipsychotic drugs, those receiving an SGA for at least three months together with any FGA regardless of treatment duration were assigned to the SGA stratum and those receiving an SGA for less than three months together with an FGA for at least three months were assigned to the FGA stratum.

Data collection

Subjects were evaluated at a single consultation with the participating investigator. The investigator completed a study questionnaire for each subject, which collected data on sociodemographic variables (age, gender, marital status, living situation, education level and employment status), lifestyle factors (smoking status, alcohol and substance use, food intake behaviour, physical activity), diagnosis, current (prior six months) and previous (earlier than six months before inclusion) antipsychotic drug treatment, comorbidities (hypertension, diabetes, dyslipidaemia and other cardiovascular disease) and family antecedents (psychosis, hypertension, diabetes, dyslipidaemia and other cardiovascular disease in a first-degree relative). During the visit, height, weight, supine blood pressure and waist and hip circumference were measured. All data were recorded on a paper case report form.

Waist and hip measurements were made using a standardised procedure. The investigator sat beside the subject, preferably wearing underclothes only, who was asked to stand with their feet fairly close together (about 12–15 cm), with their weight equally distributed on each leg and with their shoulders back. Subjects were asked to breathe normally and the measurement was made at the end of a normal exhalation, while ensuring that the subjects did not contract their abdominal muscles. Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest using a plastic metric tape held firmly in a horizontal position. The tape should be loose enough to allow the investigator to place one finger between the tape and the subject's body. Hip circumference

was measured in a similar fashion at the maximum circumference over the buttocks.

Biochemical measures

A fasting blood sample was programmed to be taken after an overnight fast within the week following the index consultation. In a subgroup of sites at which the facilities were available, an oral glucose tolerance test using a 75 gram glucose load was performed at the same time. All blood samples were analysed centrally (BARC, Gent, Belgium). The following fasting parameters were measured: glucose, insulin, HbA1c, apolipoprotein B, triglycerides, total cholesterol and high-density lipoprotein (HDL) cholesterol.

An investigator's manual in English and an instruction leaflet for handling blood samples in each language was prepared by BARC and distributed to all study sites. This covered a description of the tests to be carried out and a summary of the sampling and sample management procedures with comprehensive pictogrammes. BARC provided each site with a kit sufficient to cover six visits including blood sampling tubes, specific requisition forms for individual patients featuring colour-coded peel-off stickers for labelling the sampling tubes, isothermal transport boxes with gel packs, and airbills and IATA-compliant packaging for dispatch of material to the central laboratory. Tubes for analysis of glucose, lipids and HbA1c were to be dispatched at ambient temperature and tubes for analysis of insulin frozen at -20°C . Centres were provided with a dedicated telephone number to contact the courier for shipment. The cost of shipment was prepaid by BARC. Upon receipt of shipment, samples were inspected, and subject and visit data entered in the database. Any omissions, anomalies or inconsistencies in the data were queried immediately with a Data Clarification Form sent to the site by fax. Once the analyses had been performed, the results were faxed to the study site within 24 hours of sample reception. The results were also entered directly by BARC into the study database through a web-based electronic interface.

Outcome measures

The primary evaluation criterion was the prevalence of a glycaemic disorder. Secondary evaluation criteria were the prevalence of hyperinsulinaemia, dyslipidaemia, obesity, abdominal obesity, hypertension, hypotension. Definitions of these entities are provided in Table 1. The metabolic syndrome was defined according to the revised ATP III criteria of the National Cholesterol Education Programme

(NCEP) (Grundy *et al.*, 2005). In addition, the Framingham risk factor for coronary heart disease was derived from data collected in the study (Wilson *et al.*, 1998).

Two composite measures, related to food intake and physical activity, were created for the purposes of the study. These were derived from relevant items in the study questionnaire, each scored on Likert scales, which were summed to yield a total score. The maximum possible scores for the food intake composite and the physical activity composite were fourteen and seven, respectively, with a higher score representing a less healthy lifestyle. The psychometric validity of these two constructs was assessed using principal component analysis and estimation of Cronbach's α coefficient.

Statistical analysis

The target number of subjects to be included in the study was estimated using *a priori* power calculations based on an anticipated prevalence of glycaemic disorder of 15% (Dixon *et al.*, 2000) in order to determine this prevalence in both treatment strata with a precision of $\pm 3\%$. To achieve this goal, it would be necessary to include at least 545 subjects in each stratum. In order to reflect current antipsychotic prescription practice in Europe (IMS Health, 2006), three times as many subjects were to be included into the SGA stratum compared to the FGA stratum. The total number of subjects should thus be $(545 \times 3) + 545 = 2180$. Assuming that 15% of subjects would not be evaluable, the target study population was thus 2566. In order to permit exploratory analyses by country, it was requested that at least 100 subjects be included per country, with eight to 40 subjects per centre.

The analysis was performed on all included subjects respecting the inclusion criteria for whom evaluable data were available concerning antipsychotic treatment and duration, glycaemia and diabetes history and treatment. For the analysis of risk factors and antipsychotic drug treatment, an exploratory analysis was also performed restricted to subjects receiving a single antipsychotic drug during the previous three months. Prevalence estimates were determined with 95% confidence limits and compared between the two treatment strata.

Variables associated with the presence of a metabolic disorder were determined by multiple logistic regression analyses and the strength of association expressed as odds ratios with 95% confidence intervals. The analysis was performed in three steps. Since allocation to treatment stratum was not randomised, differences in the distribution of covariates could appear between types of treatment. For this reason, as a first step, a propensity score was

Table 1 Definition of pathologies evaluated in the study

Glycaemic disorder	One of the following: Fasting blood glucose ≥ 100 mg/dl (5.5 mM) Treatment with insulin or an oral antidiabetic drug
Hyperinsulinaemia	Serum insulin ≥ 12 mU/l
Lipid disorder	One of the following: Total cholesterol > 200 mg/dl (5.1 mM) HDL cholesterol < 40 mg/dl in men (1 mM) or < 50 mg/dl (1.3 mM) in women Apolipoprotein B > 120 mg/dL Triglycerides ≥ 150 mg/dl (1.7 mM) Treatment for a known lipid disorder
Obesity	Body mass index > 30 kg/m ²
Abdominal obesity	Waist circumference ≥ 102 cm in men or ≥ 88 cm in women
Hypertension	One of the following: Systolic blood pressure ≥ 130 mm Hg Diastolic blood pressure ≥ 85 mm Hg Treatment with an antihypertensive medication
Hypotension	One of the following: Systolic blood pressure ≤ 100 mm Hg Diastolic blood pressure ≤ 60 mm Hg
Metabolic syndrome [NCEP definition (Grundey <i>et al.</i> , 2005)]	At least three of the following Abdominal obesity (as defined earlier) Triglycerides ≥ 150 mg/dl (1.7 mM) or treated HDL cholesterol < 40 mg/dl in men (1 mM) or < 50 mg/dl (1.3 mM) in women or treated Hypertension (as defined earlier) Glycaemic disorder (as defined earlier)

calculated in order to ensure comparability of subjects between the two treatment strata (Rosenbaum and Rubin, 1983). This score was estimated using a logistic regression, including all variables represented on the case report form with the exception of those included in the definition of a metabolic disorder, weight gain and impaired fasting glucose, and those for which data was missing for more than 10 subjects. The subjects were classified into the deciles of the propensity score and their distribution across deciles compared between treatment strata.

In the second step, the association between treatment stratum and presence of a disorder was tested using a multivariate model which also included country and site, gender, age, duration of current treatment, time from diagnosis, family history of diabetes, Food Intake Composite score, Physical Activity Composite score, employment status and the propensity score classified by decile. In this analysis, subjects prescribed more than one antipsychotic medication were analysed as a separate polypharmacy treatment group, and compared to subjects receiving either FGAs or SGAs in monotherapy.

Finally, a third multivariate logistic regression analysis was performed in which type of treatment (monotherapy with an FGA, monotherapy with an SGA and polytherapy) was evaluated as a risk factor for the presence of a metabolic disorder. Confounding factors significantly associated with the disorder of interest in the previous model were also entered into the analysis. Study centre was again included as a random effect and the propensity score as a covariate. From this final model, odds ratios for the probability of presenting the disorder of interest were calculated taking monotherapy with an FGA as the reference treatment.

All statistical analyses were two-sided and a probability level of 0.05 was taken to be statistically significant.

Ethics

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment), Good Epidemiology Practice (Andrews *et al.*, 1996) and the International Epidemiology Association (IEA) European federation

guidelines for Good Epidemiological Practice, as well as pertinent national legal and regulatory requirements. Written informed consent was obtained from each subject. Subjects were free to withdraw from the study without incidence on their treatment. The protocol was submitted to and approved by the appropriate local ethics committee in each country. Confidentiality of personal data entered into the study database was ensured by replacement of the patient's name by a number and conformed to the relevant national legislation.

Role of the funding source

The study was initiated by the European Medical Affairs division of Sanofi-Aventis (the study sponsor). Since local representatives of the sponsor would be instrumental in identifying potential study centres, the study was proposed to all national affiliates of the sponsor in Europe. Participating countries thus reflect those affiliates who accepted to participate. In each country, local medical representatives of the sponsor were responsible for defining the sectorial breakdown of psychiatric health care provision, which was used to determine the distribution of centres invited to participate in each country. The local representative could also designate a psychiatrist in that country to coordinate recruitment of participating centres. All investigators recruited received fees for their participation in the study on a per patient basis.

The study sponsor designated a scientific committee to advise on the scientific and strategic direction of the study. The scientific committee (MdH, MM, KS, TW and BF) was composed of specialists in the fields of psychiatry, endocrinology, epidemiology and clinical trial methodology. The committee assisted in developing the study protocol and the statistical analysis plan, advised on the analysis and exploitation of the study results and contributed to the writing of the present article. All committee members received honoraria from the sponsor in return for their participation.

A contract research organisation, Lincoln (Boulogne, France), was mandated by the study sponsor for operational management of the study, data collection and management and statistical analysis. Based on the data analysis, Lincoln provided complete statistical tables according to the pre-specified statistical analysis plan and a clinical study report to the study sponsor, who made this available unabridged to the scientific committee. All committee members had full access to all data from the study, and could request further analyses during meetings of the scientific committee.

The study sponsor funded editorial support from a medical writing agency (Foxymed, Fresnes, France) for the

preparation of the present article and contributed, together with the scientific committee, to the revision of the different drafts of the manuscript. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

Results

Participating physicians

One hundred and eighty two physicians participated in the study. The number of participants in each country ranged from three in Romania to 27 in Bulgaria (Figure 1). Participants practiced principally in a hospital setting (64.1%) and in an urban location (86.3%). The mean duration of practice of participating physicians was 22.1 ($\pm$ 10.0) years (Table 2).

Screening log

Of the 182 selected centres, 159 included subjects in the study. In some countries, notably Turkey and Russia, the screening log was not completed in all centres. For centres completing the log, 4557 subjects were screened for participation and 2156 included (47.3%). Of the remainder, 1147 subjects refused to participate (25.2%) and 1036 (22.7%) did not fulfil the inclusion criteria. It should be noted that the proportion of screened subjects who were actually included varied markedly between countries, from 20.3% in Latvia to 85.7% in Italy (Table 3). The age, gender distribution and class of antipsychotic treatment did not differ between included and non-included subjects (Table 4). Only two (0.1%) of the non-included subjects did not fulfil diagnostic criteria for schizophrenia.

Since certain centres did not complete the screening logs as planned, case report forms were submitted for an additional 307 subjects who were not identified in the screening log, making a total of 2463 subjects providing data. The source and assignment of the different subjects included in the study is illustrated in the patient flow diagram presented in Figure 2. This total number of included subjects was close to target (2470) for all countries except Germany, where 65 subjects were included instead of 100 as planned. The number of included subjects was slightly higher than the number expected in Italy and Latvia.

For 98 of 159 active centres (61.6%), subject numbers in the screening log and in the database of case report forms matched completely and the number of included subjects was lower than the number of screened subjects. These compliant centres accounted for a total of 1501 included subjects.

Figure 1 Distribution of assessable subjects across participating countries.

Table 2 Participating physicians ($N=182$)

Geographical location	$N=146$
Urban	126 (86.3%)
Suburban	17 (11.6%)
Rural	3 (2.1%)
Type of practice	$N=145$
Hospital-based	93 (64.1%)
Community	45 (31.0%)
Mixed	7 (4.8%)
Duration of practice (years)	$N=147$
Mean $\pm$ standard deviation	22.1 $\pm$ 10.0
Median [Range]	24.0 [1.0–52.0]

Assessable subjects

Of the 2463 subjects for whom a case report form was provided, 2270 subjects (92.2%) were considered as assessable. The remaining 193 subjects were excluded due to absence of evaluable data on diabetes history or on associated treatments (115 subjects, 59.6%), absence of data on blood glucose allowing assignment of a glycaemic disorder (94 subjects; 48.7%), unstable or untreated psychotic disorder (40 subjects; 20.7%), information missing on current antipsychotic treatment and duration (20 subjects; 10.4%) and infringement of other entry criteria (four subjects; 2.1%).

Of the assessable subjects, 537 (23.7%) were assigned to the FGA treatment stratum and 1733 (76.3%) to the SGA stratum (Table 5). The target assignment ratio for the two strata was 0.75. This ratio was respected ($\pm 5\%$) in all countries except Germany (0.84), Italy (0.80) and Turkey

Table 3 Number of subjects targeted, screened, included and assessed

Country	Centres	Target	Screened	Included	CRF	Assessed	FGA stratum	SGA stratum
Bulgaria	27	500	1141	500	500	484	119	365
Czech Republic	15	200	358	167	201	163	40	123
Estonia	8	110	280	106	110	106	26	80
Germany	5	100	187	64	65	57	9	48
Greece	14	300	453	259	290	261	62	199
Italy	13	150	196	168	168	145	29	116
Latvia	22	110	577	117	127	119	29	90
Lithuania	21	200	444	200	200	195	44	151
Romania	3	100	301	100	100	92	29	63
Russia	24	400	331	276	401	383	97	286
Slovenia	9	100	97	83	101	91	19	72
Turkey	21	200	192	116	200	174	34	140
Total	182	2470	4557	2156	2463	2270	537	1733

Note: CRF, case report form; FGA, first-generation antipsychotic; SGA, second generation antipsychotic.

Table 4 Comparison of included and non-included subjects entered into the screening log

	Included (<i>N</i> = 2156)	Non-included (<i>N</i> = 2401)	Total (<i>N</i> = 4557)
Median age [range] (years)	41.0 [18–84]	42.0 [1–90]	41.5 [1–90]
Female gender	981 (45.5%)	1166 (48.6%)	2147 (47.1%)
Second-generation antipsychotic drug use	1643 (76.2%)	1784 (74.3%)	3427 (75.2%)

(0.80), where subjects prescribed SGAs were over-represented and Romania (0.68) where these were under-represented.

Antipsychotic drug treatments

The different antipsychotic drugs prescribed to participants for the previous three months are presented in Figure 3. Overall, 20 different FGAs were prescribed, although 15 of these were prescribed to less than 30 subjects each. Nearly half the prescriptions related to haloperidol (47.3% of subjects). Of the SGAs, risperidone was the most widely prescribed (25.2% of subjects). Ziprasidone, aripiprazole, sertindole and zotepine were prescribed to $\leq 5\%$ of subjects, and have been combined in an 'other SGA' group for future analyses. However, marked differences in prescribing practice were observed between participating countries (Table 5). For example, the proportion of subjects prescribed haloperidol in the FGA stratum ranged from 15.8% in Slovenia to 82.3% in Greece. In the SGA stratum, the proportion prescribed clozapine ranged

from 7.9% (Lithuania) to 44.4% (Slovenia) and the proportion prescribed risperidone from 9.5% in Romania to 44.4% in Russia.

In the FGA stratum, 443 subjects had been prescribed a single antipsychotic in the previous three months (82.5%). In the SGA stratum, the number of subjects prescribed a single treatment was 1417 (81.8%). This subset of subjects was used for the evaluation of potential associations between individual antipsychotic drugs and presence of metabolic disorders. Combinations of FGAs and SGAs were prescribed to 208 subjects, who were all assigned to the SGA stratum. The median treatment duration was 24.4 months (range: 3–258) in the FGA stratum and 17.2 months (range: 3–336) in the SGA stratum.

Sociodemographic and clinical features of the study population

The demographic and clinical characteristics of the study sample are presented in Table 6. The median age of the

Figure 2 Patient flow through the study. FGA, first-generation antipsychotic stratum; SGA, second-generation antipsychotic stratum. The 'other' group of screened subjects not included in the study corresponds to otherwise eligible subjects screened that the investigator failed to enter into the study.

population was 41.0 years (range: 18.0–87.0) and there was a slight over-representation of male subjects (over 54%). The majority were unmarried (57.5%), lived at home (87.4%) and were either unemployed or registered as unable to work (54.9%). Differences between the two treatment strata were observed for all socio-demographic variables except living status. The median age of subjects treated with SGAs was lower than those treated with FGAs [$p < 0.001$; analysis of variance (ANOVA)] and subjects in the SGA stratum were more frequently unmarried and less frequently divorced ($p = 0.007$; χ^2 test). The distribution of educational level grades was shifted towards a higher education level in subjects receiving SGAs ($p < 0.001$; χ^2 test), and these subjects were more likely to be in full- or part-time work ($p < 0.001$; χ^2 test). The clinical presentation of schizophrenia was similar in the two groups in terms of disease subtype and age on onset, although the duration of illness was significantly shorter in the SGA stratum ($p < 0.001$; ANOVA). The proportion of subjects with a first-degree relative who also presented a psychotic disorder was high (26.5%).

Metabolic and cardiovascular pathology

The proportion of subjects presenting the metabolic pathologies of interest ranged from 28.4% overall for glycaemic disorders to 69.9% for lipid disorders. The proportion of subjects who were obese was 29.4%, and 43.4%

were hypertensive. No apparent differences were observed in the frequencies of these different pathologies between the FGA and SGA strata (Table 7).

Food intake and physical activity composite scores

Data on lifestyle factors in the METEOR study population are presented in Tables 8 (food intake) and 9 (physical activity). With respect to food intake, around one-third of subjects reported eating between meals and eating or snacking whilst watching television, and around one-quarter reported eating sweets or cakes several times a day. Nearly half the population reported drinking sweet drinks at least several times a week. Nearly 20% considered themselves to be always hungry. The proportion of subjects who thought that they had put on weight in the previous year was higher ($p < 0.01$; χ^2 test) in the SGA stratum (49.5%) than in the FGA stratum (36.6%), as was the proportion who claimed that family or friends had told them that they eat too much (27.9% in the SGA stratum versus 19.0% in the FGA stratum; $p < 0.01$).

The mean score on the food intake composite measure was 4.3 ± 2.3 (median: 4) in the FGA stratum and 4.8 ± 2.4 (median: 5) in the SGA stratum. This difference in score was statistically significant ($p < 0.001$; Student's *t*-test; 95% confidence interval of difference in mean: -0.831 to -0.369).

Principle component analysis of the food intake score identified a single dominant dimension to explain the

Table 5 Individual antipsychotic prescription by country

	Bulgaria (N = 484)	Czech Republic (N = 163)	Estonia (N = 106)	Germany (N = 57)	Greece (N = 261)	Italy (N = 145)	Latvia (N = 119)	Lithuania (N = 195)	Romania (N = 92)	Russia (N = 383)	Slovenia (N = 91)	Turkey (N = 174)
FGAs	N = 119	N = 40	N = 26	N = 9	N = 62	N = 29	N = 29	N = 44	N = 29	N = 97	N = 19	N = 34
Haloperidol	31 (26.1%)	25 (62.5%)	11 (42.3%)	3 (33.3%)	51 (82.3%)	20 (69.0%)	16 (55.2%)	31 (70.5%)	8 (27.6%)	38 (39.2%)	3 (15.8%)	17 (50.0%)
Other FGAs	89 (74.8%)	27 (67.5%)	17 (65.4%)	8 (88.9%)	20 (32.3%)	11 (37.9%)	17 (58.6%)	21 (47.7%)	21 (72.4%)	59 (60.8%)	17 (89.5%)	20 (58.8%)
SGAs	N = 365	N = 123	N = 80	N = 48	N = 199	N = 116	N = 90	N = 151	N = 63	N = 286	N = 72	N = 140
Olanzapine	81 (22.2%)	36 (29.3%)	16 (20.0%)	9 (18.8%)	30 (15.1%)	30 (25.9%)	19 (21.1%)	54 (35.8%)	23 (36.5%)	42 (14.7%)	19 (26.4%)	33 (23.6%)
Clozapine	68 (18.6%)	16 (13.0%)	14 (17.5%)	19 (39.6%)	35 (17.6%)	30 (25.9%)	19 (21.1%)	12 (7.9%)	12 (19.0%)	35 (12.2%)	32 (44.4%)	38 (27.1%)
Quetiapine	42 (11.5%)	19 (15.4%)	20 (25.0%)	3 (6.3%)	26 (13.1%)	12 (10.3%)	14 (15.6%)	19 (12.6%)	2 (3.2%)	25 (8.7%)	9 (12.5%)	13 (9.3%)
Risperidone	59 (16.2%)	23 (18.7%)	22 (27.5%)	14 (29.2%)	57 (28.6%)	26 (22.4%)	27 (30.0%)	30 (19.9%)	6 (9.5%)	127 (44.4%)	7 (9.7%)	39 (27.9%)
Amisulpride	86 (23.6%)	11 (8.9%)	2 (2.5%)	7 (14.6%)	54 (27.1%)	14 (12.1%)	15 (16.7%)	31 (20.5%)	13 (20.6%)	39 (13.6%)	4 (5.6%)	15 (10.7%)
Other SGAs	29 (7.9%)	28 (22.8%)	8 (1.0%)	14 (29.2%)	42 (21.1%)	14 (12.1%)	9 (10.0%)	8 (5.3%)	7 (11.1%)	20 (7.0%)	7 (9.7%)	14 (10.0%)

Note: Since subjects could be prescribed more than one antipsychotic, the categories are not mutually exclusive. FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

variance in the data with an eigenvalue of 2.6. No other dimension presented an eigenvalue greater than unity. The standardised Cronbach's α coefficient for the internal consistency of the individual items of the score was 0.66.

With respect to the physical activity items, around one-third of subjects claimed not to go out of the house every day, not to cook and to watch television every day. Three-quarters of the subjects reported to practice a sport or other physical activity several times a week. For the physical activity composite score, principal component analysis identified no dominant dimension to organise the data and it was not possible to reduce the items to fewer dimensions than the number of component items (four). Eigenvalues for the four dimensions retained ranged from 0.8 to 1.4. The standardised Cronbach's α coefficient was 0.34. Given the lack of validity of the measure, mean scores and inter-group differences for this measure and not presented.

Discussion

The METEOR study represents the first large-scale attempt to determine the prevalence of metabolic disorders in patients with schizophrenia in Europe and to evaluate the relationship between such disorders and antipsychotic drug treatment. The study included 2270 subjects in 12 countries, principally in Eastern Europe. The clinical features of these patients are consistent with what would be expected for European patients with schizophrenia, although the proportion of patients for whom a family history of psychosis was reported is higher (26.5%) than what would be expected from previous studies (Byrne *et al.*, 2002; Gottesman, 1991; Mortensen *et al.*, 1999). There is a lack of recent epidemiological data on schizophrenia in many of the participating Eastern European countries and the study thus provides novel information on schizophrenia and its treatment in these countries, in addition to the data on metabolic disorders.

The proportion of subjects presenting the pathologies of interest in the study was relatively high, ranging from 28% for glycaemic disorders to 70% for lipid disorders. No marked difference in frequencies was observed between the two antipsychotic treatment strata. The relationship between the presence of different metabolic disorders and potential risk factors, including treatment assignment, as well as adjusted prevalence rates, will be presented in a future article.

An issue for the design of the study was the generalisability of the study population, in order to extend the findings to patients with schizophrenia in participating countries in general. The sequential inclusion of subjects fulfilling the entry criteria consulting spontaneously the

Figure 3 Antipsychotic drug treatments. Left: first-generation antipsychotic (FGAs) drugs; right: second-generation antipsychotic (SGAs) drugs. The 'Other FGAs' group consists of 15 drugs each prescribed to less than 30 subjects. Since individual subjects could receive more than one drug, classes are not mutually exclusive (410 subjects received multiple antipsychotics).

study centre for whatever reason, together with stratification of subjects treated with FGAs or SGAs should have optimised the representativity of patients with respect to participating centres. However, it cannot be excluded that the rather high proportion (25.2%) of screened subjects who declined to participate in the study may introduce a bias. For example, subjects with metabolic disorders may have been more likely to consent to participate or encouraged their psychiatrists to do so, thus possibly inflating the prevalence of metabolic disorders estimated in this study.

Concerning the representativity of study centres with respect to psychiatric practice, this cannot be guaranteed. Complete representativity cannot be achieved in studies in which investigators have to agree to participate, and a bias always exists as practice standards of investigators who are interested enough in the study question to wish to participate may not be representative. Another issue is that physician registries allowing a random selection of physicians for participation in such epidemiological studies do not exist in many of the participating countries. The choice of physicians was thus made according to the personal experience of the study coordinator in each country. Although centres were supposed to be chosen operationally to reflect psychiatric practice in each country, no specific method was prescribed for achieving this, and there was no way to ensure that this was actually achieved. It should also be noted that the number of study centres, and thus the number of subjects recruited, do not reflect the demographics of participating country, for example 200 subjects included in Lithuania compared to 65 in Germany. The countries participating in the study represent those

European countries in which the local affiliate of the study sponsor was interested in participating in the study.

The use of web-based patient log to ensure accurate and timely recruitment and stratification of subjects was helpful, and enabled 87% of the target study sample to be recruited within the planned recruitment period. However, certain centres in Russia and Turkey did not use the screening log at all, and others did not record all subjects in their log. For future studies, quality could perhaps be improved by providing more information on the utility and use of a screening log before the start of inclusion.

Another aspect of the study that was considered important to standardise was the laboratory assessment of blood samples. Given the wide geographical dispersion of the study sites and the associated heterogeneity in approaches to laboratory testing of metabolic variables, it was decided to implement all testing in a central laboratory with a long experience of such measures in psychiatric populations, allowing benchmarking of the data obtained against the historical database. This decision required mechanisms to be put in place to allow timely and safe dispatch of blood samples across borders outside the open customs area of the European Union.

An important goal of the study was to evaluate a wide range of potential confounding factors for metabolic disorders. In particular, height, weight, waist circumference and blood pressure were all measured directly during the consultation and a blood sample taken for measurements of serum lipids and glucose. Such information is impossible to obtain in the type of large registry studies that have been performed to evaluate the relationship between

Table 6 Socio-demographic and clinical features of included subjects

	FGA stratum (<i>N</i> = 537)	SGA stratum (<i>N</i> = 1733)	Total (<i>N</i> = 2270)	<i>p</i>
Age, median [range] (years)	46 [18–87]	39 [18–79]	41 [18–87]	<0.001
Gender (female)	249 (46.4%)	782 (45.1%)	1031 (45.4%)	0.613
Marital status	<i>N</i> = 536	<i>N</i> = 1733	<i>N</i> = 2269	0.007
Married	136 (25.4%)	425 (24.5%)	561 (24.7%)	
Divorced	109 (20.3%)	253 (14.6%)	362 (16.0%)	
Single	280 (52.2%)	1024 (59.1%)	1304 (57.5%)	
Other	11 (2.1%)	31 (1.8%)	42 (1.9%)	
Living situation	<i>N</i> = 536	<i>N</i> = 1731	<i>N</i> = 2267	0.271
At home	460 (85.8%)	1521 (87.9%)	1981 (87.4%)	
In sheltered housing	47 (8.8%)	143 (8.3%)	190 (8.4%)	
Other	29 (5.4%)	67 (3.9%)	96 (4.2%)	
Education level	<i>N</i> = 537	<i>N</i> = 1731	<i>N</i> = 2268	<0.001
None	4 (0.7%)	8 (0.5%)	12 (0.5%)	
Primary school (1–5 years)	60 (11.2%)	104 (6.0%)	164 (7.2%)	
High school (6–9 years)	130 (24.2%)	362 (20.9%)	492 (21.7%)	
Secondary school (10–12 years)	224 (41.7%)	750 (43.3%)	974 (42.9%)	
College/university (13–16 years)	107 (19.9%)	462 (26.7%)	569 (25.1%)	
Post graduate (>16 years)	12 (2.2%)	44 (2.5%)	56 (2.5%)	
Unknown	None	1 (0.1%)	1 (<0.1%)	
Employment status	<i>N</i> = 536	<i>N</i> = 1689	<i>N</i> = 2266	<0.001
Working full-time	38 (7.1%)	248 (14.3%)	286 (12.6%)	
Working part-time	34 (6.3%)	158 (9.1%)	192 (8.5%)	
House-wife	21 (3.9%)	73 (4.2%)	94 (4.1%)	
Inapt to work	261 (48.7%)	687 (39.7%)	948 (41.8%)	
Unemployment	70 (13.1%)	227 (13.1%)	297 (13.1%)	
Retired	97 (18.1%)	255 (14.7%)	352 (15.5%)	
Never worked	15 (2.8%)	82 (4.7%)	97 (4.3%)	
Type of schizophrenia diagnosis	<i>N</i> = 518	<i>N</i> = 1689	<i>N</i> = 2207	0.029
Paranoid schizophrenia	411 (79.3%)	1258 (74.5%)	1669 (75.6%)	
Undifferentiated schizophrenia	40 (7.7%)	135 (8.0%)	175 (7.9%)	
Disorganised schizophrenia	26 (5.0%)	76 (4.5%)	102 (4.6%)	
Schizophreniform disorder	15 (2.9%)	55 (3.3%)	70 (3.2%)	
Other	26 (5.0%)	161 (9.5%)	187 (8.5%)	
Paranoid schizophrenia + other	0 (0.0%)	4 (0.2%)	4 (0.2%)	
Age at diagnosis, median [range] (years)	27 [7–80]	26 [4–65]	26 [4–80]	0.097
Duration of illness, median [range] (years)	15.4 [0.2–51.0]	10.0 [0.0–57.0]	11.0 [0.0–57.0]	<0.001
Family history of psychosis	142 (26.5%)	458 (26.5%)	600 (26.5%)	0.736

Note: FGA, first-generation antipsychotic; SGA, second-generation antipsychotic. Data was missing on sociological variables for one subject in the FGA stratum, for subtype of schizophrenia diagnosis for 18 subjects in the FGA stratum and 44 subjects in the SGA stratum, and on age at diagnosis and duration of illness for six subjects in the FGA stratum and 25 in the SGA stratum.

schizophrenia and metabolic disorders that have been carried out previously in North America. Lifestyle factors are also well-characterised risk factors for the development of metabolic disorders, but information on these is not generally available from previous studies of patients with schizophrenia.

In the METEOR study, these lifestyle factors were evaluated using a questionnaire and an attempt was made to generate a composite score to evaluate these. Around one-third of subjects reported 'unhealthy' food habits such as eating between meals or snacking in front of the television. The food intake composite measure appeared to have

Table 7 Frequency of evaluated pathologies in subjects treated with first or second generation antipsychotic drugs

	FGA stratum (<i>N</i> = 537)	SGA stratum (<i>N</i> = 1733)	All subjects (<i>N</i> = 2270)
Glycaemic disorders	167 (31.1%)	478 (27.6%)	645 (28.4%)
Lipid disorders	377 (70.2%)	1204 (69.5%)	1581 (69.6%)
Obesity	145 (27.0%)	522 (30.1%)	667 (29.4%)
Abdominal obesity	243 (45.3%)	846 (48.8%)	1089 (48.0%)
Hypertension	254 (47.3%)	732 (42.2%)	986 (43.4%)
Metabolic syndrome	182 (34.0%)	587 (34.2%)	769 (33.9%)

Note: FGA, first-generation antipsychotic; SGA, second-generation antipsychotic.

Table 8 Food intake composite measure

	Food intake composite	Score	FGA (<i>N</i> = 537)	SGA (<i>N</i> = 1733)
Q1	During the last 12 months, did you drink sweet drinks?		<i>N</i> = 533	<i>N</i> = 1730
	Never	0	92 (17.3%)	273 (15.8%)
	A few times each month	1	195 (36.6%)	639 (36.9%)
	Several times a week	2	148 (27.8%)	503 (29.1%)
	Every day	3	98 (18.4%)	315 (18.2%)
Q2	Do you eat three meals a day?		<i>N</i> = 537	<i>N</i> = 1732
	Yes	0	429 (79.9%)	1453 (83.9%)
	No	1	108 (20.1%)	279 (16.1%)
Q3	Do you eat between meals?		<i>N</i> = 533	<i>N</i> = 1728
	No	0	308 (57.8%)	1163 (67.3%)
	Yes	1	225 (42.2%)	565 (32.7%)
Q4	Do you eat or have snacks while watching television?		<i>N</i> = 536	<i>N</i> = 1730
	No	0	383 (71.5%)	1142 (66.0%)
	Yes	1	153 (28.5%)	588 (34.0%)
Q5	Do family or friends ever tell you that you eat too much?		<i>N</i> = 537	<i>N</i> = 1731
	No	0	435 (81.0%)	1248 (72.1%)
	Yes	1	102 (19.0%)	483 (27.9%)
Q6	Do you always have sweets or cakes on hand?		<i>N</i> = 536	<i>N</i> = 1732
	No	0	437 (81.5%)	1386 (80.0%)
	Yes	1	99 (18.5%)	346 (20.0%)
Q7	Do you eat sweets or cakes several times a day?		<i>N</i> = 537	<i>N</i> = 1733
	No	0	432 (80.4%)	1683 (31.0%)
	Yes	1	105 (19.6%)	503 (29.0%)
Q8	Do you take snacks with you when you go for a walk?		<i>N</i> = 536	<i>N</i> = 1730
	No	0	501 (93.5%)	1579 (91.3%)
	Yes	1	35 (6.5%)	151 (8.7%)
Q9	Are you always hungry?		<i>N</i> = 536	<i>N</i> = 1733
	No	0	446 (83.2%)	1392 (80.3%)
	Yes	1	90 (16.8%)	341 (19.7%)
Q10	Do you think that you have put on weight over the past year?		<i>N</i> = 535	<i>N</i> = 1732
	No	0	339 (63.4%)	874 (50.5%)
	Yes	1	196 (36.6%)	858 (49.5%)

Table 9 Physical activity composite measure

	Physical activity composite	Score	FGA (N = 537)	SGA (N = 1733)
Q1	Do you go out of the house?		N = 537	N = 1728
	Every day	0	348 (64.8%)	1201 (69.5%)
	Two or three times a week	1	124 (23.1%)	366 (21.2%)
	Two or three times a month	2	35 (6.5%)	92 (5.3%)
	Less often than twice a month	3	30 (5.6%)	69 (4.0%)
Q2	At home, do you cook or do housework?		N = 537	N = 1729
	Yes	0	180 (33.5%)	523 (30.2%)
	No	1	357 (66.5%)	1206 (69.8%)
Q3	Do you practice a sport or other physical activity?		N = 537	N = 1729
	Several times a week	0	440 (81.9%)	1341 (77.6%)
	Once a week	1	64 (11.9%)	224 (13.0%)
	Never	2	33 (6.1%)	164 (9.5%)
Q4	Do you watch television?		N = 536	N = 1725
	Never	0	41 (7.6%)	113 (6.6%)
	Two or three times a week	1	130 (24.3%)	382 (22.1%)
	Every day	2	365 (68.1%)	1230 (71.3%)

satisfactory internal consistency and a unidimensional factorial structure. The mean score on this scale was significantly higher, corresponding to more 'unhealthy' eating habits in the SGA stratum than in the FGA stratum. With respect to individual items, subjects in the SGA group more frequently reported putting on weight and that their entourage had told them that they ate too much. This composite measure may thus be an interesting and sensitive tool to evaluate eating habits in populations at risk for metabolic disorders. The measure deserves further validation in future dedicated studies. In contrast, the psychometric properties of the physical activity composite measure were not satisfactory.

The need to take into account other confounding factors when assessing any relationship between antipsychotic drug treatment and the prevalence of metabolic disorders required an appropriate statistical method. We chose to use the propensity adjustment method (Rosenbaum and Rubin, 1983) for this purpose, which is now widely used in pharmacoepidemiological studies to control for non-random allocation of subjects between two groups of interest, and thus minimise potential bias due to imbalance between the groups. Propensity scores estimate the probability that a subject has been allocated to a particular treatment from a vast list of variables and this probability is then used to adjust the estimate of the treatment effect. The larger the number of potential confounding variables included in the score, the lower the risk of residual bias due to unobserved or unknown covariates

in the final estimate of the treatment effect. For the primary analysis, we initially chose to use a dichotomous categorisation of drug treatments into an FGA group and an SGA group in order to optimise the statistical power for detecting any between-class differences. A disadvantage of this approach was that each group could be 'contaminated' by patients receiving multiple antipsychotic drug treatments including both FGAs and SGAs. For this reason and, in view of the rather high proportion of patients receiving polypharmacy (14.1%), which was not anticipated, an additional *post hoc* analysis was also performed in which a 'mixed' polypharmacy category has been compared to either FGA monotherapy or SGA monotherapy.

Antipsychotic prescription patterns were somewhat different from those expected from previous pharmacoepidemiological studies in Western Europe (Gasquet *et al.*, 2005; Hanssens *et al.*, 2006; Ren *et al.*, 2002), and large inter-country differences were observed. In particular, the use of clozapine was higher than anticipated, 19% overall and up to 44.4% in Slovenia, and the rate of prescription of olanzapine particularly low (14.7%) in Russia.

As with all such studies, the METEOR study has a number of strengths and limitations. The principal strengths are the respectable number of subjects included, the wide geographical coverage, the range of risk factors evaluated and the limited amount of missing data. In addition, the study population was fairly similar in terms of demographic features and clinical presentation to that

evaluated in the CATIE study (Nasrallah *et al.*, 2006), which will provide an opportunity to compare our European data with the findings of this important recent North American study. Limitations of the study include the cross-sectional design, which precludes addressing the causality of any associations observed, the possibility that outpatients were not fasting when blood sample was taken, and potentially incomplete or inaccurate data collection on somatic morbidities and treatment history by the psychiatrist. Although the range of risk factors investigated was extensive, certain potentially important risk factors were not considered, such as psychopathology [for example Positive and Negative Syndrome Scale (PANNS) scores], or may be inadequately reported, such as treatments prior to six months before inclusion. In addition, the involvement of a study sponsor who markets an antipsychotic medication (amisulpride) may have led to unintentional bias, for example in the selection of study centres. We chose to evaluate cardiovascular risk using the Framingham risk factor score, as this is a well-established method for which considerable benchmark data is available. However, it should be recognised that this algorithm was developed and validated in the United States. Although it might have been more appropriate to use a European composite measure such as SCORE (Conroy *et al.*, 2003), the weighting of risk factors in SCORE is country-specific and not available for all participating countries, with the consequence that data obtained with this measure cannot be pooled across countries. In contrast, with the Framingham risk factor score, the same analysis can be performed on the whole dataset in a

uniform way. In addition, at the time the statistical analysis plan was designed, little published normative data obtained using SCORE had been published. Finally, differences in the regulations and criteria for approval in ethics committees in different countries of Eastern Europe may have influenced which centres participated in the study and which subjects were included.

In conclusion, the METEOR study represents a large-scale attempt to collect data on the relationship between schizophrenia, its treatment and metabolic disorders in Europe, which has emerged as a major issue in the management of patients with schizophrenia over the last decade. The study used a cross-sectional design aimed at overcoming the methodological limitations of previous North American studies of this issue, and at providing complementary information to these latter important studies. Consistent with the findings of these previous studies, the proportion of subjects with schizophrenia in the METEOR population in whom metabolic disorders were detected was high.

Declaration of interest statement

This study was sponsored and funded by Sanofi-Aventis. All members of the study group have received honoraria from the sponsor for participation in the study as well as, in some cases, consultancy fees in the previous three years. All authors had full access to all data from the study, and the corresponding author, had final responsibility for the decision to submit the finalised manuscript for publication. AG is an employee of Sanofi-Aventis.

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