Assessing the prevalence of the Metabolic Syndrome according to NCEP ATP III in Germany: feasibility and quality aspects of a two step approach in 1550 randomly selected primary health care practices

Bestimmung der Prävalenz des Metabolischen Syndroms nach NCEP ATP III in Deutschland: kleine Machbarkeit und Qualitätsaspekte eines zweistufigen Erhebungsansatzes in 1550 zufällig ausgewählten hausärztlichen Praxen

Abstract

Objective: Metabolic Syndrome (MetSyn) describes a cluster of metabolic disorders and is considered a risk factor for development of cardiovascular disease. Although a high prevalence is commonly assumed in Germany data about the degree of its occurrence in the population and in subgroups are still missing. The aim of this study was to assess the prevalence of the MetSyn according to the NCEP ATP-III (National Cholesterol Education Program Adult Treatment Panel III) criteria in persons aged ≥18 years attending a general practitioner in Germany. Here we describe in detail the methods used and the feasibility of determining the MetSyn in a primary health care setting.

Research design and methods: The German-wide cross-sectional study was performed during two weeks in October 2005. Blood samples were analyzed in a central laboratory. Waist circumference and blood pressure were assessed, data on smoking, life style, fasting status, socio-demographic characteristics and core information from non-participants collected. Quality control procedures included telephone-monitoring and random on-site visits. In order to achieve a maximal number of fasting blood samples with a minimal need for follow-up appointments a step-wise approach was developed. Basic descriptive statistics were calculated, the Taylor expansion method used to estimate standard errors needed for calculation of confidence intervals for clustered observations.

Results: In total, 1511 randomly selected general practices from 397 out of 438 German cities and administrative districts enrolled 35,869 patients (age range: 18-99, women 61.1%). More than 50,000 blood samples were taken. Fasting blood samples were available for 49% of the participants. Of the participating patients 99.3% returned questionnaires to the GP, only 12% were not filled out completely. The overall prevalence of the MetSyn (NCEP/ATP III 2001) was found to be 19.8%, with men showing higher prevalence rates than women (22.7% respective 18.0%).

Conclusions: This study was designed to provide data as robust as possible within the confines of an epidemiological study. Judging by the low degree of missing data and the high data quality, the feasibility for this kind of a research setting (short evaluation period, practitioners as data assessment sites) was found to be very good. The results will help to gain a more comprehensive insight into the prevalence of MetSyn for patients in primary health care in Germany.

Keywords: Metabolic Syndrome X, primary health care, cross-sectional study, prevalence study, family practice, Germany

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**Zusammenfassung**

**Hintergrund:** Das Metabolische Syndrom (MetSyn) umschreibt einen heterogenen Symptomenkomplex - Hyperglykämie, Hypertonie, reduziertes HDL-Cholesterin, Hypertriglyceridämie sowie abdominelle Adipositas - der mit einem erhöhten Risiko für kardiovaskuläre Morbidität und Mortalität assoziiert wird. Epidemische Zunahmen des Syndroms werden aus den USA und anderen Ländern berichtet. Auch in Deutschland wird von einer starken Ausbreitung des Syndroms ausgegangen, allerdings fehlen hier genaue epidemiologische Daten. Ziel der Studie ist eine bundesweite Querschnittserhebung der Prävalenz des MetSyn gemäß NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III)-Kriterien bei Frauen und Männern ab 18 Jahren in allgemeinärztlichen Praxen. Schwerpunkt dieses Beitrages ist die Beschreibung methodischer Aspekte, insbesondere hinsichtlich Machbarkeit in hausärztlichen Praxen, Verfahren zur Nüchternbestimmung und Qualitätsaspekten.

**Methoden:** Die deutschlandweite, versorgungsepidemiologische Prävalenzstudie wurde in zwei Wochen im Oktober 2005 bei einer Zufallsstichprobe von hausärztlichen Praxen durchgeführt. Erfasst wurden BMI, Taillenumfang, Blutdruck, Blutzuckerschnelltest (finger prick), Serumglukose und -lipide sowie Angaben zu Lebensstil, Vorerkrankungen, Familienanamnese, Medikation, soziodemografischen Merkmalen. Minimalinformationen von Nichtteilnehmern wurden erhoben. Qualitätskontrollen umfassten Telefonmonitoring sowie Onsite visits. Ein spezielles Verfahren minimiert die Zahl der Wiedereinbestellungen aufgrund von Nüchternbestimmungen. Deskriptive Statistiken wurden mit SAS 9.2 erstellt, die Taylor Methode zur Schätzung des Standardfehlers zur Kalkulation von Konfidenzintervallen für geclusterte Beobachtungen angewendet.

**Ergebnisse:** Insgesamt wurden bei 1511 Allgemeinarztpraxen in 397 von 438 Landkreisen und kreisfreien Städten 35.869 Patienten eingeschlossen (Altersrange: 18-99, Frauen: 61.1%). Mehr als 50.000 Blutproben wurden analysiert, davon 49% als Nüchternbestimmung. Die Gesamtprävalenz des MetSyn liegt bei 19.8%, Männer weisen höhere Prävalenzen auf als Frauen (22.7% respektive 18.0%).

**Schlussfolgerung:** Mit der Studie können erstmals bundesweite Zahlen zur Prävalenz des Metabolischen Syndrom nach der genauen NCEP ATP III-Definition vorgelegt werden. Die Qualität der erhobenen Daten überstieg die Erwartungen. Der stepwise approach führte zu einer hohen Wiedereinbestellungsquote. Soweit einschätzbar konnten systematische Fehlerquellen mittels des robusten Studiendesigns in Grenzen gehalten werden. Insgesamt erweitern die Daten dieser Studie den Wissensstand in Deutschland um das Metabolische Syndrom und dessen konstituierenden Einzelfaktoren in hausärztlichen Praxen. Nachfolgende Analysen ermöglichen Prävalenzbestimmungen auch nach den neueren Definitionen des Metabolischen Syndroms.

**Introduction**

Metabolic Syndrome (MetSyn), also known as insulin resistance syndrome, Syndrome X or Deadly Quartet, describes a combination of metabolic disorders that have been found to be associated with an increased risk of cardiovascular disease (CVD), and overall mortality [1], [2], [3], [4]. Several different definitions for MetSyn are in use [5], all involving increased blood pressure, abdominal obesity, increased serum triglycerides and lowered HDL cholesterol as major parameters. Differences among the definitions include the valuation of hyperglycemia, insulin resistance or glucose intolerance. Currently the most accepted definitions are those of the World Health Organization (WHO) [6], the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [7], and the recently modified definitions by the American Heart Association (AHA)/National Heart, Lung and Blood Institute (NHLBI) [8], [9] and the International Diabetes Federation (IDF) [10], with the main difference being...
diabetes as a prerequisite for the diagnosis of MetSyn in the WHO definition but not in the NCEP ATP III/AHA/NHLBI-definition, as well as different cut points of dichotomized risk factors, inclusion of drug treatment for hypertension and triglyceridemia, and central obesity as a necessary requirement for the diagnosis of the MetSyn [10]. However, since no insulin levels have to be determined when using the NCEP ATP III, AHA/NHLBI-definition for diagnosis, this approach is easier to apply for epidemiological studies as well as in primary health care practices and is therefore the most widely used. MetSyn is common in persons with abdominal obesity, and it is considered an independent risk factor for CVD [11]. However, this is not without controversy. Since only 3 out of 5 criteria have to be met for MetSyn diagnosis according to NCEP guidelines, there are 16 different conceivable combinations of risk factors that cannot be weighted equally in terms of predictive importance for CVD [12]. It has even been reported that the excess risk of CVD in patients with MetSyn is only due to diabetes and is independent from all other criteria, [13]. What is known for sure is that the cardiovascular risk increases disproportionately with coexistent arterial hypertension [14]. Epidemiologic studies have shown that the prevalence of MetSyn varies depending on the different definitions of WHO and NCEP [15]. Although there is no consistent information, combined data from Germany, the USA and Finland give a rough estimate of MetSyn prevalence in the range of 10%-25% among 35-70 year olds [16], with a higher frequency in men than women. First indications on the MetSyn prevalence in Germany result from an analysis approaching the NCEP definition [17]. Nevertheless, detailed information about the MetSyn in Germany is limited.

The objective of our study was to assess the MetSyn prevalence according to the NCEP ATP III-definition (2001) in a primary health care setting in Germany during a 2 week assessment period. All patients ≥18 years of age attending their primary health care physician for general health issues at randomly selected sites were examined in the course of a single morning on all 5 criteria of the MetSyn. In order to achieve a maximal number of fasting blood samples with a minimal need for follow-up appointments a stepwise approach was developed. Since this study was conducted in October 2005, the study protocol and study material had to be finished in the beginning of 2005, half a year before the release of the IDF- and updated AHA/NHLBI-definitions. For this reason the most widely used NCEP ATP III-definition was chosen here to estimate the MetSyn as primary outcome variable. Nevertheless in secondary analysis it is planned to calculate and compare the different definitions published recently.

The purpose of this paper is to describe in detail the methods used and evaluate the feasibility of screening patients in primary health care settings when patients visited for routine care, particularly with regard to problems of achieving fasting blood samples, the very short evaluation period, missing data and data quality.

Methods

Study design and participating physicians

We conducted a 2-week cross-sectional prevalence study. General practitioners and internists with focus on primary health care (both henceforth abbreviated as GP) were selected by a stratified, randomized sampling method to receive a random distribution across all German regions. Medical practices specialized in cardiology and/or diabetes were excluded from the study. Physicians were contacted once by mail and informed about the background and aims of the study. They were asked to complete a fax questionnaire indicating their consent to participate in the study (or to give a reason for non-participation). The fax response further included site information about personal data, specialization of the GP as well as equipment of the site, especially with respect to the survey requirements. In case of non-contact or non-response, no further recruitment effort was made.

Study population

The study population comprised all male and female patients ≥18 years of age who visited their GP at the participating sites on the day of the survey (regardless of the reason for visiting) and who gave their written informed consent for participation. The only reasons for exclusion were conditions that made it impossible or highly problematic for the patient to participate (such as poor German language skills, serious disabilities or diseases), acute emergences, or pregnancies and breast-feeding within the previous 3 months. The study protocol did not allow for further selection of patients. All patients who were eligible on the given day were included consecutively. At each site, the participating GPs and their staff assessed the individual criteria for MetSyn and basic data on socio-demography, anamnesis and life style in the course of a single morning (except for the recruitment group “young”, for which the survey was extended to a whole day, see below) using questionnaires, materials and procedures provided for the study.

Non-response

To rule out that non-response resulted in a biased sampling of participants, age group (<45 years, 45-59 years and ≥60 years of age), sex, reason for attendance of the medical practice, obesity (as judged by the physician or the nurse), risk of coronary heart disease (as judged by the physician or the nurse), and reason for non-response in the study were documented for patients who did not give their informed consent for participation.
Two-stage approach

Since food intake has an impact on serum glucose and triglyceride levels, which are important criteria in determining MetSyn, a two-stage approach was applied for blood sampling. First, all patients on the predetermined examination day were included regardless of fasting status. By using a blood glucose (BG) quick test, it was possible to directly exclude or diagnose hyperglycemia, independent of the patient’s fasting state, based on the selected capillary BG concentration cut points of <5.56 or >11.11 mmol/L. If the findings concerning fasting serum glucose or triglycerides were ambiguous due to a meal in the previous 8 respective 12 hours, the patient was asked to come for a second appointment to give a fasting blood sample. Furthermore, a random sample (30%) of participants was asked to come for a second fasting blood sample, regardless of the first test result (see below Sampling strata for recruitment of study participants). These data provided useful information about intra-individual variations, e.g. regression-to-the-mean effects.

Ethical approval

Ethical approval was granted from the ethics committee of the University Hospital, University Duisburg-Essen, Essen, Germany.

Pre-study

Due to the complexity of the survey and for sample size calculation purposes, a pre-study was performed. The pre-study already used all components of the main study, including the clinical research organization (CRO), the central laboratory, site recruitment and patient sampling. The survey instruments included the questionnaires and laboratory analyses.

Information was collected on the following in the pre-study:
- Response rate and participation of GPs
- Quality of information material for GPs and their employees
- Recruitment of patients
- Time frame for examinations
- Quality of questionnaires in terms of completing validity and understanding
- Logistic courses/communicational structures (especially laboratory logistics).

Timeline

A pre-study was conducted in June 2005 and the main study followed in October 2005. The second referrals and return of completed questionnaires were finished on December 2nd 2005, and double data entry was finished by the end of December 2005. Data quality checks and the creation of a scientific database were completed by the end of March 2006.

Sample size calculation

Calculations for determination of the study population size were based on basic assumptions (as outlined below), on results and experiences of the pre-study, and on the strategy of recruitment. The sample size calculation was aimed to get even numbers of patients in six strata defined by sex and age group (<45 years, 45-59 years and ≥60 years of age).

Basic assumptions

Calculations of the number of patients to be included were based on the following data and assumptions:
- In the expected range of prevalence p per age group and sex a precision of 100 • d = 2% was to be accomplished, with d = 1.96•(p•(1-p)/n)^½ being the half-width of the 95% confidence interval of the binominal distribution of the prevalence p at samples size n.
- The distribution of age and sex in a random sampling at participating sites were gathered from the pre-study.
- The drop-out rate of recruited patients due to incomplete or implausible statements was estimated to be 20%.

Consideration of pre-study results

- Number of participants and valid observations with respect to MetSyn
  In the pre-study, the survey was conducted at 25 participating sites. From 772 patients whose age and sex were specified, 619 patients met all inclusion criteria and participated in the study. A total of 497 patients could be evaluated regarding MetSyn, and for 362 patients all 5 criteria of the MetSyn could be evaluated (for evaluation, 3-4 criteria are sufficient if at least 3 criteria are positive or 3 criteria are negative). Therefore, the study yielded an average of 24.8 participating patients per site, and an average of 19.9 patients per site could be assessed with respect to MetSyn. The number of patients was different in the separate strata defined by age and gender. Both men and women 60 years andolder were enrolled more often than men and women of younger age groups: for those ≥60 years, 108 men and 140 women could be assessed, but only 36 men and 86 women <45 years, and 50 men and 77 women in the age group of 45-59 years. This information helped to optimize the recruitment strategy in the main study with respect to age groups.
- Effects of monitoring
  In the pre-study, 18 out of 25 participating sites were attended by specifically trained monitors, the other 7 sites were not monitored. On average, fewer participants (17% less) were recruited at sites without monitoring. However, due to the small number of sites and a high variation in the number of patients docu-
mented at each site (between 0 and 50), deviations in either direction are difficult to interpret. In the main study about 10% of the sites were attended by monitors. Therefore, it was expected that the average number of participating patients per site in the main study would be approximately 15% less than in the pre-study. This overall average included the assumption that some sites would fail to participate at all.

Given these considerations and the recruitment group design described below, a total of 35,000 participants were to be enrolled at 1660 sites in the 2-week period. In this way an even distribution of patients were to be achieved in three age strata, and the estimated prevalence for age group and gender would have the desired precision (95% confidence interval width of ±2% or smaller) in each stratum.

**Sampling strata**

**Sampling strata for recruitment of medical health care sites**

Considering an estimated response rate of 10%, approximately 17,000 sites had to be contacted and asked for participation in order to obtain the targeted number of sites and patients. A regionally stratified random sample of addresses was provided by Schwarzeck Verlag (Ottobrun, Germany).

The number of GPs in each stratum (10 postal regions identified by the first digit of the postal code) was proportional to the number in the address base. In the pre-study, physicians’ response and participation were not systematically related to region, age or sex, and therefore potential non-response bias appeared to be unlikely.

**Sampling strata for recruitment of study participants**

To perform an optimal recruitment strategy, 3 sampling strata or recruitment groups were created:

1. **Recruitment group 1: normal**

All participating patients in this group were examined and asked for a blood sample. In case the findings for fasting serum glucose or fasting serum triglycerides were ambiguous due to a meal in the previous 8 hours (serum glucose) or 12 hours (serum triglycerides), the patient was asked to come for a second appointment to give a fasting blood sample, possibly within the following 2 weeks.

2. **Recruitment group 2: sample**

Patients in this group were asked to give a second fasting blood sample within the following days, independent of their fasting state and findings from the blood sample on the day of the survey. Data of patients in this group who gave fasting blood samples at both visits are used to estimate intra-individual day-to-day variations of the BG and triglyceride concentrations as well as to confirm the results and conclusions drawn from the BG quick test and to ensure its usability.

In the pre-study, only 45% of the patients who had been asked to give a second blood sample actually returned for the second appointment. Additionally, approximately 20% of the data sets lacked some data. As the goal was to obtain a second blood sample for 3200 participants (approximately 10% of the total study population), approximately 8800 patients had to be scheduled for a follow-up appointment (8800 x 45% x 80% = 3200).

3. **Recruitment group 3: young**

Results of the pre-study had shown that the age group of ≥60 years of age was the most represented in the study population. The least represented was the group of men <45 years of age, followed by men and women between 45-59 years of age. To ensure an accurate determination of MetSyn prevalence in the underrepresented younger age groups, only patients <60 years of age were recruited in a subset of participating medical practices. In order to allow for sufficient numbers of patients in the survey, recruitment was extended to a whole day for this group.

500 sites were assigned each to the recruitment groups 1 and 2. A total of 21,000 patients were expected to participate at these 1000 sites. 660 sites were assigned to the recruitment group 3, with a targeted 14,000 participants. GPs were assigned randomly to the 3 recruitment groups. After the study, not all sites submitted data even after a reminder by mail or phone to submit the results. This problem had been predicted and included in the sample size calculation.

**Procedure of the survey**

Recruitment of GPs:

- Approximately 17,000 sites were selected randomly and contacted once by mail between August 29 and September 12, 2005, to briefly inform them about the study and request their participation.
- Every participating GP was assigned a survey date.
- 1-2 weeks prior to begin of the study, participating GPs received 2 packages including detailed information material, questionnaires, documentation forms and laboratory material.
- A telephone hotline was run by the CRO and the central laboratory starting from the day of the first mail contact.
• Each participating site was given a “wake-up call” 2-3 days prior to the respective survey day to remind the GP and his/her employees about the study and the planned survey day and to acknowledge the receipt of information and laboratory materials.

Recruitment of study participants:
• According to the assigned recruitment group, each physician was to enroll all consecutive men and women presenting for routine care regardless of the reason (prescriptions, check-ups, etc.), either within a single morning (recruitment groups 1 and 2) or over the course of an entire day (recruitment group 3). Each doctor had received questionnaire forms for a maximum of 50 patients, which seemed sufficient for most sites (23 out of 25 sites in the pre-study contributed less than 50 patients). If the number of patients was less than 50, the doctor was asked to return the unused questionnaire forms along with the completed ones.
• Core information for all non-responders was to be documented on a standardized questionnaire.
• To eliminate or reduce the bias of selecting risk patients, the physicians should not select patients, but instead include all patients on an otherwise “normal” day. The patients learned about the study only after entering the physician’s practice on the day the study was conducted.

Follow-up appointment
If a non-fasting BG concentration of 5.56-11.11 mmol/L or a non-fasting blood triglyceride concentration of ≥1.71 mmol/L of the venous blood sample was determined (see below), the patient had to be scheduled for a follow-up appointment to collect a second, fasting venous blood sample. At the follow-up appointment the patient was again questioned about the intake of the last meal and last drink and the blood pressure was measured. In sites belonging to the recruitment group 2 (“sample”), all patients were asked to return for a follow-up appointment for a second, fasting blood sample.

Data collection

Questionnaires
The medical questionnaire (examination form) was to be completed by the GP or his/her assistant and the following information about the patient was to be documented:
• Age (month and year of birth), sex, reason for attendance of the medical practice (according to question 32D of the Germany Health Survey, [18]), reason for refusal to participate in the study (if applicable).
• Blood pressure, body weight, body height, waist circumference, blood sample data.
• Type and time of the last meal and drink.
• Pre-existing cardiovascular diseases (CHD, esp. myocardial infarction, angina pectoris, stroke, peripheral arterial occlusive disease [pAVK], cardiac insufficiency).
• History of diabetes (type 1 or 2).
• Other major diseases (hypertension, metabolic disorders, thyroid disorders, gout, liver disorders, cancer).
• Medication (antidiabetics, methyl dopa, beta-blockers, diuretics, lipid reducers, corticosteroids, thyroid hormones, high dosage acetyl salicylic acid [>2 g/d], high dosage ascorbic acid [>0.4 g/L], thyrostatics).

The patient questionnaire contained questions concerning
• Age, sex
• Medical history
• Time since last doctor visit, frequency of doctor visits in the past 4 weeks
• Smoking habit (including former smoking habit and year of quitting)
• Exercise and physical fitness (according to questions 61, 64 of the BGS98 [18])
• Nutrition (general habits according to abbreviated question 53, 58 of the BGS98 [18], current and previous diets, last meal/drink)
• Family anamnesis
• Pregnancy status
• Sociodemography (education, occupation and marital status according to the German Demographic Standard [19]).

The main goal was to obtain the highest possible rate of completed, high quality forms. The number of questions was thus reduced to a minimum to minimize the number of patients who might refuse to participate because they considered the questionnaires to be too demanding. According to pre-study results, the patients completed the questionnaires within 5 to 30 minutes, with an average of 10 minutes.

Blood pressure
Blood pressure was measured in a sitting position after a 5-minute rest with the equipment commonly available in the medical practice. Accepted epidemiologic standards for blood pressure measurement (triple measurement, at least 10 minutes recovery) could not be met in this case.

Waist circumference
Waist circumference was measured with the provided common tape measures at the narrowest point between the last rib and the highest part of the iliac crest. For obese patients the last rib and the highest part of the iliac crest were palpated manually and measurement was performed at half distance between both positions.
Blood sampling

An initial screening BG quick test from a capillary (finger stick) sample was performed with every patient and the results were documented in the reporting form. Additionally, for each patient, venous blood samples were collected and shipped within 24 hours to the central laboratory (Labor 28, Berlin, Germany) by an assigned courier service. The blood samples were analyzed for levels of glucose, LDL-cholesterol, HDL-cholesterol, total cholesterol and triglycerides. GPs were equipped from the central laboratory with pre-labeled natriumfluorid-(NaF) and serum tubes for taking the samples.

Blood glucose

Note that BG data were collected in mg/dL, but are reported here using the SI units of mmol/L. The initial capillary BG quick test was performed to identify all patients with a BG concentration of <5.56 mmol/L or those with a BG concentration of ≥11.11 mmol/L. These 2 groups were not required to be assigned for a second visit. Only BG levels between 5.56 mmol/L and 11.11 mmol/L did not allow an immediate assessment of the BG status, so these patients were scheduled for a follow-up visit within the following 2 weeks to provide a second, fasting blood sample. This step-wise approach considerably reduced the need for follow-up appointments. Furthermore, those subjects requiring a follow-up visit were told that their findings were ambiguous and that the second blood sample was necessary to properly assess their medical condition. The aim was to increase the patients’ motivation to return for the second appointment and thus to increase the number of patients with fasting blood samples.

Triglycerides

Initial blood triglyceride concentrations in the venous blood samples below 1.71 mmol/L (150 mg/dL) were considered normal, and fasting values of 1.71 mmol/L or higher were considered elevated. In both cases, no further blood sample was necessary. However, initial non-fasting values of 1.71 mmol/L or higher required confirmation from a second fasting blood sample to distinguish between a high lipid concentration due to a previous meal or due to dyslipidemia.

Blood analysis

All samples were analyzed by Labor 28 AG, Berlin, using Roche Hitachi MODULAR systems. Plasma glucose levels from blood in the NaF tube were estimated by the glucose-6-phosphate dehydrogenase method (G6P-DH). Triglyceride levels from blood in the serum tube were estimated by the enzymatic color test. If the level was >11.43 mmol/L (1000 mg/dL), the analysis was repeated with a reduced volume. In both cases, control kits used were Roche Precinorm U and Precipath P and calibration was conducted at least 3 times a day. Total cholesterol, HDL-cholesterol and LDL-cholesterol levels were estimated by enzymatic color tests.

Quality assurance

Guidelines

The study was planned and performed according to the German guidelines for Good Epidemiology Practices (GEP) and the respective standard operating procedures (SOPs) of the Institute for Medical Informatics, Biometry and Epidemiology, as far as the latter were relevant for epidemiological studies.

Monitoring concept

To reduce the logistics of coordinating such a large, country-wide study, participating GPs received no other instructions than the information material sent to them by mail prior to the survey. To control for a proper procedure and to ensure the robustness of the data obtained, a specifically adapted monitoring system was designed to meet the high logistic needs. This monitoring concept included telephone-monitoring and random on-site visits. The monitors were specifically trained prior to start of the study, especially in terms of survey procedures in the different recruitment groups and criteria for follow-up appointments.

Telephone monitoring

Telephone monitoring was performed at 50% or more of the enrolled sites prior to the day of the survey to ensure all participating physicians had the complete and correct set of forms, documents and blood sampling materials available on the survey day. Additionally, the knowledge of the employees concerning the project was checked to avoid systematic errors that might have had a direct influence on the primary target value (prevalence of MetSyn), e.g. by selective appointment of potential MetSyn risk patients. Physicians to be included in telephone monitoring were selected randomly but stratified by the 3 recruitment groups. To guarantee a standardized interview, a questionnaire with 15 questions was provided. After the phone call the interviewers rated the monitored site based on the interview results. For rating, particular emphasis was placed on the following issues which led to lower ratings:

- Refusal of the telephone monitoring
- Referral of risk patients
- Procedure for follow-up appointment not (correctly) known
- Usage of the documents very unclear (at least 2 wrong answers out of 4 questions)
- Inclusion criteria wrong
On-site visits

On-site visits were performed on the day of the survey, with a focus on quality of data and measurements. Monitoring visits were planned in at least 10% of the participating medical practices. A priori, these practices were chosen at random though proportional to the 3 recruitment groups. Some sites that received a poor rating after the telephone monitoring were to be specifically included in the on-site monitoring, if possible. The observed quality problems and errors at the monitored sites allowed an estimation of the overall error rate of the study. For example, data from sites that did not follow the inclusion rules could be compared to data from sites where the instructions were followed precisely to estimate the possible extent of selection bias.

Major issues of on-site monitoring were:

- Correct completion, signature and dating of the informed consents
- Correct measurement of all parameters
- Inclusion of all eligible patients
- Integrity of the questionnaire data
- Correct follow-up procedures in the different recruitment groups

If possible, 5 questionnaires from the GP as well as 5 questionnaires from patients were to be checked for integrity. The GP assistants were requested to rectify observed errors. The data base contained a FAQ list that was continuously updated.

Data entry

Shipment of the questionnaires was organized by the participating CRO (IFE, Germany, Essen). Data were entered manually as double entry (using Proc Compare) from the questionnaire by the CRO. During data entry, automatic plausibility controls (e.g. range checks) were conducted. Data handling was specified by the CRO’s SOPs. The CRO delivered a raw data set including documentation, that was checked for errors according to predefined plausibility checks. All data entry forms were checked for plausibility and integrity as well as for compliance with inclusion- and exclusion criteria. All data sets were checked for incorrect data and corrected if applicable; all corrections were documented and double checked by a second person. All data sets were submitted for biostatistic analysis.

Data analysis

Sensitivity analyses and additional quality measures

The estimates were checked for potential bias by sensitivity analysis. Incomplete data, especially with respect to the criteria of MetSyn, were analyzed using imputation analysis and a comparison of available case analysis versus complete case analysis. The effect of the corrections was analyzed by a comparison of raw data versus corrected data analysis. With respect to fasting time, the effect of a potential recall bias on the part of the interviewees was analyzed by using different time limits for fasting status, and also a comparison of fasting data versus random data. The effect of non-response and sampling error was analyzed with an age and gender standardization.

Diagnostic conventions

The criteria for MetSyn were defined in accordance with NCEP ATP III conventions as published in 2004 (see Table 1). Diabetes was defined as the patient having diabetes according to either the current doctor’s diagnosis, or the patient’s declaration, or the use of diabetes medication. History of CVD was based on the doctor’s anamnesis. Additional risk factors like diet, smoking, activity habits and family history of myocardial infarction and coronary disease were defined based on the patient’s self-reported data in the standardized patient questionnaire.

Statistics

For the main variables of the study, basic descriptive statistics, number of observations, mean, standard deviation, median (complemented by standard deviation of the mean, lower and upper quartile as well as 5% and 95% quantiles, minimum, maximum, and 95% confidence interval for the population mean) were calculated. The sample population (patients) was drawn from sampling units (= physicians’ practices). The observations were clustered because of similar sites. This had consequences for statistical calculations, e.g. the calculation of confidence intervals. Here we used the Taylor expansion method [20], [21] with the SAS procedures SURVEYFREQ (for tables of frequencies) and SURVEYMEANS (for means), which is a well accepted method for analysis of clustered samples. All statistical analyses were conducted using the statistical software package SAS 9.1 (SAS Institute, Cary, NC, USA).
Table 1: Diagnosis of the Metabolic Syndrome according to definitions of NCEP ATP III and AHA/NHLBI*

| Risk factor       | NCEP ATP III, 2001 [7] | AHA/NHLBI, 2004 [8] | AHA/NHLBI, 2005 [9] |
|-------------------|------------------------|----------------------|---------------------|
| Central Obesity   | Waist                  | Waist                | Waist (Europids)    |
|                   | M >102 cm (>40 in)     | M >102 cm            | M ≥102 cm**         |
|                   | W >88 cm (35 in)       | W >88 cm             | W ≥88 cm            |
| Blood pressure    | ≥130 mm Hg systolic    | ≥130 mm Hg systolic  | ≥130 mm Hg systolic |
|                   | blood pressure or      | blood pressure or    | blood pressure or   |
|                   | ≥85 mm Hg diastolic    | ≥85 mm Hg diastolic  | ≥85 mm Hg diastolic |
|                   | blood pressure         | blood pressure       | blood pressure or   |
|                   |                        |                      | antihypertensive drug treatment in a patient with a history of hypertension |
| Fasting Glucose   | ≥6.1 mmol/L (110 mg/dL) or known Diabetes | ≥5.6 mmol/L (100 mg/dL) or known Diabetes | ≥5.6 mmol/L, or known Diabetes |
| Triglyceride (TG) | ≥1.7 mmol/L (150 mg/dL) | ≥1.7 mmol/L (150 mg/dL) | ≥1.7 mmol/L, or drug treatment for elevated TG |
| HDL-Cholesterol   | M <1.0 mmol/L (40 mg/dL) | M <1.0 mmol/L        | M <1.0 mmol/L       |
| (HDL-C)           | W <1.3 mmol/L (50 mg/dL) | W <1.3 mmol/L        | W <1.3 mmol/L or treatment for HDL-C |

*M: Men; W: Women
*often cited as NCEP ATP III definitions (2004, 2005)
**changed from “>” to “≥”

Results

Participating primary health care practices

Of the 17,271 primary health care practices contacted, 2600 responded to the invitation to participate in the study (15% response). The response rate varied slightly in the different postal code areas but no differences greater than +/-2% between contacted and participating sites for each region could be observed (Table 2). The first 2070 response faxes were collected and analyzed for eligibility. These revealed 1835 eligible physicians out of which the first 1700 were recruited for participation. Among these, 140 cancelled their participation before starting the study, mainly due to time-related issues, communication problems or illness. 33 of the 1835 originally eligible physicians were recruited in a second run to replace cancellations among the 1700. One physician was found to be on the recruitment list twice. 81 physicians did not return the survey material despite a reminder sent to them by mail, which reduced the final number of participating sites to 1511.

Monitoring

Telephone monitoring

Out of 1046 attempted calls, 913 sites could be included in the evaluation of the telephone monitoring. This outnumbered the targeted 50% of the 1600 sites that had been aimed for recruitment by n=124. The interview was refused at 42 sites, e.g. due to a lack of knowledge on the topic/absence of the responsible person (12 sites), lack of time (8 sites) and other, mainly organizational reasons (such as postponement or cancellation of the survey day; 11 sites). In 2 sites general disinterest in the interview was expressed and 3 sites did not consider the telephone to be a suitable medium of communication. Most sites were rated 3 or 4 (with 1 being best and 6 being worst) in the telephone monitoring, as shown in Figure 1. The distribution of ratings was similar in the 3 recruitment groups.
On-site visits

185 on-site visits were performed out of which 20 were not successful. 10 sites were visited due to their bad rating (rating 5 or 6) in the telephone monitoring; 2 of these sites decided not to participate in the study on short notice.

In 27 sites not all patients who attended the practice were included in the study and in 9 cases patients were not properly informed about the study. Mistakes in the recruitment strategy were observed in only 3 cases.

Data quality

About 38% of the individuals with casual capillary blood levels or individuals in recruitment group 2 ("sample") did not return for the required fasting blood sample test. However, among the patients who did return for the follow-up appointment, the percentage of fasting blood samples (≥12h fasting) increased from 17.0% at the survey day to 62.7% at the referral (Figure 2). Differences between individuals who returned for the follow-up ap-

Table 2: Distribution of sites by postal regions (ohne Markierung)

| Region | Contacted physicians | Participating physicians |
|---|---|---|
| | n₁ | (%) | n₂ | (%) | response % (=n₂/n₁) |
| 0 | 1362 | 7.9 | 134 | 8.9 | 9.84 |
| 1 | 1537 | 8.9 | 153 | 10.1 | 9.95 |
| 2 | 1739 | 10.1 | 149 | 9.9 | 8.57 |
| 3 | 1934 | 11.2 | 153 | 10.1 | 7.91 |
| 4 | 2000 | 11.6 | 195 | 12.9 | 9.75 |
| 5 | 1847 | 10.7 | 151 | 10.0 | 8.18 |
| 6 | 1556 | 9.0 | 132 | 8.7 | 8.48 |
| 7 | 1843 | 10.7 | 146 | 9.7 | 7.92 |
| 8 | 1872 | 10.8 | 137 | 9.1 | 7.32 |
| 9 | 1581 | 9.2 | 161 | 10.7 | 10.18 |
| Total | 17271 | 100.0 | 1511 | 100.0 | 8.75 |

Figure 1: Rating of sites after telephone monitoring by recruitment group (ohne Markierung)
99.3% of the participating patients returned self-completed questionnaires to the GP. About 12% were not filled out completely. 84.1% of patients reported no problems with the questionnaire, while 10.1% found the questionnaire difficult to read (they needed glasses), 1.8% said it was difficult to answer some questions, and 7.8% said that another person helped them to complete the questionnaire (multiple responses possible).

Figure 2: Fasting status of participants at survey day respective day at referral

Figure 3: Number of non-eligible, non-responding and participating patients

Participating patients

A total of 47,924 patients visited the participating sites on the respective survey day. 5516 of these patients were not eligible to participate in the study for several reasons (Figure 3). Out of the eligible 42,408 patients, 6539 (15.4%) did not give their informed consent to participate in the study, which resulted in inclusion of 35,869 patients (85.6% response rate). Incomplete data were collected for 6527 patients.

The gender and age group distribution of patients in the main study as well as the relative distribution in the pre-study is shown in Table 3. The recruitment process optim-
Table 3: Number of participants per stratum defined by age and gender in the main-study compared to the pre-study

| Age-group | Men     |         | Women    |         | Total   |         |
|-----------|---------|---------|----------|---------|---------|---------|
|           | Main study | Pre-study | Main study | Pre-study | Main study | Pre-study |
|           | n | % | n | % | n | % | n | % | n | % |
| <45       | 4173 | 11.6 | 48 | 7.7 | 8012 | 22.3 | 97 | 15.7 | 12185 | 34.0 | 145 | 23.4 |
| 45 - 59   | 4794 | 13.4 | 87 | 11.0 | 7308 | 20.4 | 90 | 14.5 | 12102 | 33.7 | 158 | 25.5 |
| 60 - 99   | 4975 | 13.9 | 68 | 21.8 | 6607 | 18.4 | 182 | 29.4 | 11582 | 32.3 | 317 | 51.1 |
| Total     | 13942 | 38.9 | 251 | 40.5 | 21927 | 61.1 | 369 | 59.5 | 35869 | 100.0 | 620 | 100.0 |

Table 4: Prevalence of the Metabolic Syndrome according to NCEP ATP III and AHA/NHLBI1* definitions

|                | NCEP ATP III, 2001 [7] |         | AHA/NHLBI, 2004 [8] |         | AHA/NHLBI, 2005 [9] |         |
|----------------|------------------------|---------|---------------------|---------|---------------------|---------|
|                | n | % (95% CI) | n | % (95% CI) | n | % (95% CI) |
| Men (n=13942)  | 2897 | 22.68 (21.8-23.5) | 3168 | 25.10 (24.2-26.0) | 4348 | 34.20 (33.2-35.2) |
| Women (n=21927)| 3711 | 17.98 (17.3-18.6) | 3954 | 19.32 (18.6-20.0) | 5008 | 24.41 (23.6-25.3) |
| Total (n=35869)| 6608 | 19.78 (19.2-20.4) | 7122 | 21.53 (20.9-22.2) | 9356 | 28.16 (27.4-30.0) |

CI: confidence interval; *often cited as NCEP ATP III-definitions (2004, 2005)

The number of participants was evenly distributed among the age and gender strata in the main study. However, a majority of participants (61.1%) were women.

Table 4 shows the overall and sex- and age-stratified prevalence of the MetSyn depending on the MetSyn-definition used. According to the original NCEP ATP III definition (2001), the prevalence in the study population was 19.8% (men 22.7%, women 18.0%). Using the AHA/NHLBI definition from 2004, with a lower threshold for fasting glucose being the only change to the NCEP/ATP III 2001 definition, the prevalence was 21.5% (men 25.1%, women 19.3%). The newest AHA/NHLBI definition from 2005 resulted in the highest prevalence with 28.0% (men 34.3%, women 24.2%). This is because the 2005 definition includes treatment of elevated lipids and hypertension, whereas the 2001 and 2004 definitions did not include diabetes treatment only.

Discussion

Screening for MetSyn was performed in primary health care setting when patients attended for routine care. The study yielded a high data quality and a large proportion of complete data sets, especially considering the fact that the survey was performed under normal every day conditions at the medical practices.

In developed countries such as Germany, 90% of the adult population see their physicians on a regular basis [22]. Additionally, the primary health care physician can obtain appropriate consent and easily follow up on the patient in case of abnormal results.

The pre-study applied in this study enabled an a priori assessment of some of the potential pitfalls in applying the survey and in the study strategy. It proved to be a suitable tool to estimate the response rate of the sites and enabled an even distribution of different age classes in the main study.

Although the actual number of participating physicians (1511) in the main study was slightly below the targeted 1600, this was compensated by the high number of documented patients per site when compared with the pre-study results. Considering the short survey period, the single contact for initial recruitment of physicians and the fact that approximately 700 physicians who gave their...
consent for participation were not used, the number of participating sites is to be considered as very high. Data quality was enhanced by a two-step monitoring concept that improved the recruitment efficacy (as shown by the pre-study) and helped to reveal problems and difficulties that could be remedied during the survey period, thereby ensuring the integrity of the data sets. Most questionnaires (88%) were returned completely filled out. This high percentage was achieved by using short, standardized questionnaires that could be completed by the patients in an average of 10 minutes. By keeping the questionnaires short, all data necessary to assess the primary target criteria, the MetSyn according to NCEP ATP-III, could be collected from a large number of patients in a relatively short time. Overall, a high level of completeness and comparability was achieved with a reasonable amount of effort.

MetSyn is diagnosed by evaluation of fasting BG, triglycerides, HDL cholesterol, blood pressure and waist circumference. The analysis of blood samples was thus an essential parameter of the survey, and in particular the consideration of the quality of measurements made under non-standardized conditions. Methods for determination of BG are well established. However, individual biological and pre-analytical factors such as meal intake, body constitution and activity, delay between taking of the blood sample and sample processing, centrifugation and stabilizing additives, and duration and temperature of storage can have an important impact on the results [23]. Because the study was performed in the course of general medical practice activities, no highly standardized, optimized conditions such as keeping the blood samples at 4 °C and immediate centrifugation [24] could be achieved. It is known that at room temperature the glucose concentration in venous blood declines at 0.33 mmol/L per hour, independent of the original BG concentration [24]. To account for this, blood samples were collected into tubes containing the glycolysis inhibitor NaF, which ensured that the samples could be stored at room temperature (15 - 25 °C) for up to 24 hours [25]. Since medications such as novaminsulfone and ascorbic acid in concentrations of >0.4 g/L as well as α-Methyldopa at a concentration of >0.2 g/L can cause a decrease of the BG level by up to 50% [26], these kinds of medication had to be documented by the GPs. Although there is an ongoing controversy regarding the importance of measuring BG in the fasting state or not, in studies concerning the diagnosis of MetSyn fasting BG is usually measured to comply with the NCEP and WHO definitions. To date, we are aware of only one study that used random BG measures to study MetSyn [27]. However, it is generally known that the need for patients to be fasting complicates study procedures and logistics and can potentially reduce the recruitment rate. In addition, it is not possible to reliably control the fasting state as patients might not declare snacks and caloric drinks because they are unaware that these also influence the BG concentration. As a result, BG levels are often spuriously considered fasting and are misinterpreted. Thus, the high logistic and temporal efforts necessary to obtain fasting blood samples in epidemiologic studies involving a large study population renders them less suitable for opportunistic case findings in primary care. In contrast, random BG testing has been proposed as the most efficient method for use in an integrated screening program in such cases [28]. Due to the recruitment strategy in this study, patients were not necessarily fasting when they came to their appointments. Thus, relatively few fasting BG or triglyceride samples were obtained (20%). The majority of fasting blood samples available were those taken from subjects scheduled for follow-up appointments for this purpose. As it was expected that at least 40% of patients would not keep a second appointment, which would result in an increase of the required study population size and costs, the study was specifically designed to only schedule a second visit for a subgroup of patients (if their non-fasting BG was 5.56 to 11.11 mmol/L or triglycerides were >1.71 mmol/L, or those subjects in the “sample” recruitment group). This stepwise strategy enabled a targeted collection of fasting samples, which reduced the burden and complexities associated with obtaining fasting data and streamlined the study design.

Furthermore, those subjects requiring a follow-up visit were told that their findings were ambiguous and that the second blood sample was necessary to clarify their diabetic status. By formulating the request for a second visit in this way, compliance for the follow-up visit was improved as the patients had a genuine concern about their own health status.

In contrast to glucose, the fasting state for blood triglyceride determination is not specified in the definitions for MetSyn diagnosis, although it can be argued that it should also ideally be done under fasting conditions. The high individual variance of the blood triglyceride concentration is mainly influenced by the time and way of food intake prior to having the blood sample taken, and a fasting period of 10-14 hours considerably reduces the variability of serum triglycerides [29]. However, other factors such as age, sex, circadian rhythm, physical activity, smoking, alcohol consumption, and state of disease also have an influence on blood triglyceride concentration. Random effect model estimates from approximately 30 different studies published between 1970 and 1992 have shown the biological variability of total cholesterol to be 6%, of HDL to be 7.4%, of LDL to be 9.5%, and of triglycerides to be 22.6% [30]. It is thus astonishing that none of the MetSyn definitions available state the time period for fasting that is considered to be sufficient to yield serum glucose and triglyceride values that are unaffected by previous caloric intake. There is no discussion in the literature as to whether an 8 hour fast is sufficient, or if a 10, 12 or 14 hour fast is required to achieve precise and reliable values for the diagnosis of the MetSyn. Limitations of this study include the potential lack of representativeness of the sites and the population screened. The response rate of 15% of the invited sites...
might not have been enough to represent the overall situation. However, selection of the study sites was randomized and stratified by region to avoid a geographical bias. The proportion of participating sites was similar within the different postal code areas (Table 2). Regional differences in the GP participation rate could be the effect of random variation. The sample of GPs participating in the study was a good representation of the total set of GPs in Germany with respect to gender, age and the proportion of non-specialized internists. The low response rate could be the result of the recruitment process with one single contact (mail to GP), the very short time given for response (2 weeks) and the strict limitation to conduct the study on one given day.

This study could not obtain data for the population of individuals who did not visit a practitioner during the recruitment period. Germany has a publicly funded health care system for physician services with almost no user fees (except €10 for all visits in one given quarter). Thus, access to primary care physicians is not hindered by financial obstacles. According to Grabka and co-workers [31], the introduction of fees did not have an effect of discriminating persons of low social status or changing the preference to visit the physician in certain months more than in others, but instead had the beneficial effect of reducing redundant physician visits.

There may be doubts as to whether patients attending their physician are representative of the whole population. Some patients meeting MetSyn criteria might avoid attending their physician because they are in denial, in this case an underestimation of the prevalence would have been occurred. On the other hand, the estimated prevalence might be too high because the healthy population does not routinely visit their physician, although this problem was partially eliminated by excluding sites specialized in cardiology and/or diabetes. However, according to Kohler and Ziese [32], 91.8% of the adult persons in Germany consult a general practitioner during one year. Systematic non-response of patients could also lead to biased results. According to the physicians’ documentation of eligible patients on the respective survey day, the number of non-responders was 6539 compared to 35,869 responders, which would indicate a response rate of 84.6%. This is well comparable i.e. with the nationwide Second Dutch National Survey of General Practice with a response rate of 76.5% for the census and 64.5% for the health interview, yielding an age and gender distribution similar to the Dutch population [33]. Since we assessed core information of the non-responders (e.g. age group, gender, reason for visit), we were further able to analyze the potential bias caused by non-response in more detail.

In conclusion, this study was designed to provide data as robust as possible within the confines of an epidemiological study. The design and methodology enabled the collection of good quality data from 35,869 patients at 1511 primary health care practices throughout Germany within a 2-week period. In this regard the study strategy was highly successful and the data collected have the potential to provide some of the first detailed information on the prevalence of MetSyn in adults in Germany attending a general practitioner.

Notes

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SM planned and performed the study and wrote the manuscript. JH participated in the design of survey instruments, performed the statistical analysis and participated in writing the manuscript. MN participated in the sample size calculation and statistical analysis. KHJ supervised scientific, ethical and data privacy issues of the study and participated in the study design. JW participated in the study design, PA coordinated financial and administrative issues of the whole study project. All authors read and approved the final manuscript.

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