Obstructive sleep apnea (OSA) is a chronic disorder characterized by repeated upper-airway collapse during sleep, resulting in intermittent hypoxia, fragmented sleep, fluctuations in blood pressure, and increased sympathetic nervous system activity [1]. In the early 1990s in the USA, population studies found OSA-defined by an apnea-hypopnea index (AHI) higher than five events per hour-in 9% of women and 24% of men, respectively [2]. Later reports demonstrated an increased prevalence (17% of middle-aged women and 34% of men), which was primarily attributed to increased body mass index (BMI) in general populations over the last decades [3]. Remarkably, on the basis of the recent hypopnea definitions of the American Academy of Sleep Medicine (AASM) [4], the largest European epidemiologic study to date (the HypnoLaus Study) showed that 61% of women and 84% of men had OSA based on the polysomnographic AHI cut-off level of five events/h in an unselected general cohort of 2121 adults [5]. The authors concluded that the prevalence (the HypnoLaus Study) showed that 61% of women and 84% of men had OSA based on the polysomnographic AHI cut-off level of five events/h in an unselected general cohort of 2121 adults [5]. The authors concluded that the prevalence of OSA at 13.7% on the basis of the Berlin questionnaire [7], and excessive daytime sleepiness (EDS) 5.4% on the basis of the Epworth Sleepiness Scale (ESS) [8].

Accumulated research data suggest that OSA with concomitant EDS is associated with neurocognitive dysfunction and reduced quality of life [9] as well as with increased risk for traffic accidents [10]. It may also lead to cardiovascular diseases (CVD) including systemic hypertension, coronary artery disease (CAD), cardiac failure, arrhythmias, and stroke [11,12]. The first choice of treatment for OSA is positive airway pressure (PAP), which is efficient in reducing EDS and...
improving the quality of life [9]. However, as the majority of the patients with CVD do not report EDS, adherence to PAP treatment in the recent randomized controlled trials has been challenging [13,14]. Clinical phenotypes of OSA have been demonstrated to differ on the basis of anatomical [15] or physiological [16] features or a mixture of both [17]. The degree of EDS, gender differences in the presentation of symptoms, and comorbid conditions may considerably vary [18]. Moreover, among individuals who otherwise had normal total AHI values [19], OSA during rapid eye movement (REM) sleep has been shown to be associated with hypertension, indicating that this subgroup of patients deserves attention with regard to CVD outcomes [20].

With the identification of OSA as a health burden, there has been a continuous increase in the referrals to sleep centers worldwide, and numerous clinical and research protocols have been initiated to better understand the outcomes of the diagnostic and treatment procedures for the patients with OSA. In this context, the European Sleep Apnea Database (ESADA) is the largest ongoing project to date that has already recruited an enormous cohort of patients referred to sleep centers in Europe [21] for the evaluation of suspected OSA, and several reports have been published for cross-sectional and longitudinal associations of OSA with different clinical phenotypes and comorbidities [18,22-28]. The majority of the patients in the ESADA cohort were diagnosed with home sleep testing (cardiorespiratory polygraphy), and it has been emphasized that as compared with patients investigated using polysomnography [26], the individuals investigated using polygraphy are likely to have a 30% lower AHI on average.

In Turkey, the clinical management and initiation of treatment of the patients with OSA rely on in-hospital polysomnography investigations, but not much is known regarding the cross-sectional and longitudinal outcomes of the patients with OSA nationwide. One single-center, retrospective study has demonstrated gender differences in symptoms and polysomnographic features of the patients with OSA [29], and two single-center studies prospectively addressed the compliance with PAP treatment [30,31]. However, to date, there has been a lack of collaborative national network for answering the challenging research questions regarding the OSA phenotypes and metabolic and CVD outcomes as well as traffic accidents and the impact of treatment.

**Objectives**

The main aim of the Turkish Sleep Apnea Database (TURKAPNE) study is to generate a cross-sectional nationwide database for defining clinical and polysomnographic characteristics of the patients with OSA in Turkey. The primary outcomes will be the prevalence and incidence of metabolic, pulmonary, and CVD in OSA phenotypes. The association of the OSA severity indices such as AHI and oxygen desaturation index (ODI) during REM sleep and non-REM sleep with diabetes mellitus and CVD will be explored. Secondary outcomes will include gender differences in clinical symptoms, comorbidities, and polysomnographic features as well as association with traffic accidents. Moreover, adherence to PAP treatment will be evaluated. The incidence of CVD and mortality will be further addressed as long-term outcomes.

**MATERIALS AND METHODS**

**The Study Design**

The TURKAPNE study is a national, multicenter, observational, prospective cohort study, which was initiated in October 2017. The study duration for the primary outcomes is estimated to be 3 years for the first results with goal to include at least 10,000 participants during a total follow-up period of at least 10 years for all secondary outcomes. Additional subprotocols will be developed when necessary, especially in collaboration with national researchers within the other disease groups associated with OSA.

**The Study Population**

The inclusion and exclusion criteria are shown in Table 1, and the study protocol is outlined in Figure 1. All patients are recruited from the sleep centers of the university and research hospitals in Turkey. For acquiring full cross-sectional sample, patients are included irrespective of concomitant medication and degree of sleepiness as well as comorbidity, except the conditions summarized in the exclusion criteria. Information on anthropometric data, educational status, driving license, smoking habits, alcohol use, comorbidities, drug use, questionnaires, polysomnographic, and/or cardiorespiratory polygraphic findings are recorded in a systematized web-based report form. For supervising the data collection and analysis and for resolving any practical issues associated with the study, a scientific core committee was formed (YP, OKB, HF), and additionally, different joint scientific working-groups comprising representatives from the different participating centers are being formed for coordinating and direct-
ing all scientific issues associated with the ongoing protocols for the primary and secondary outcomes.

**Ethical Considerations**
Patients with suspected OSA who are referred to the participating sleep centers are invited to participate in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee of the Medical Faculty of the Marmara University, Istanbul (approval nr: 09.2016.311). All patients provided written informed consent. The study was registered with the ClinicalTrials.gov (NCT02784977).

**Data Collection and Data Quality Assurance**
The TURKAPNE project uses a specifically designed web-based data collection system constructed for transferring data to the central database www.turkapne.org at a server hosted by Hetzner Online GmbH localized in Jestetten, Germany. Each center is provided with a personal login to a clinical report format (CRF) module containing seven predefined submodules for recording data. Each sleep center has complete access to stored data on its own participants. The registry of the participants is coded and the identity of the patients is kept at the reporting sleep center and secured with a written participant identity log. A detailed protocol describing the methods for data sampling, calculation, and reporting has been distributed to all participating sleep centers. Data quality and completeness will be randomly checked by an independent study monitor with full access to the complete database. The TURKAPNE web report format will be open for new and specific CRF modules for specific sub-studies for specific patient groups, such as diabetes mellitus, pulmonary diseases, CVDs, and neurological disorders as well as for health economy evaluations that may be introduced by the participating sleep centers within the TURKAPNE network.

**Database**

**Anthropometric data, comorbidities, and concomitant medication**
Mandatory variables for each entry include information on age at diagnosis, sex, marital and educational status, driving license, smoking and alcohol habits, height, weight, circumference of the neck, waist and hip, heart rate, and systolic and diastolic blood pressure, and menstrual/menopausal status in women. A medical history including comorbidities as well as information on all ongoing medications is assessed. If taken, blood tests including blood glucose, lipids and other biochemical markers as well as lung function tests and echocardiography measurements are optionally included. Other biomarkers of interest, if already taken, can be optionally entered.

**Questionnaires, excessive daytime sleepiness**
Marital status, educational status, information on driving license, estimated driving distance (km/yr), accident history during the last three years, smoking habits, and alcohol use...
are included in the modules. Self-reported sleep latency and sleep duration as well as the ESS questionnaire containing eight questions for addressing the chance of dozing-off under eight different scenarios in the past month [8] are also included. For further evaluating and validating the OSA phenotypes in the Turkish sleep clinic cohorts, a more detailed questionnaire containing 16 questions related to symptoms associated with OSA with rating scores 1 (never), 2 (sometimes), 3 (often), 4 (very often) is optionally added. The database will be expanded for other already validated specific questionnaires when necessary.

Polygraphic and polysomnographic findings
In cases with diagnostic cardiorespiratory polygraphy data, information regarding the number of channels used, estimated sleep time, AHI, ODI (3%), average and minimum oxygen saturation time spent on supine position, and supine-AHI are documented. In clinical routines and as presently required by the Turkish Ministry of Labor and Social Security, an overnight polysomnography is obligatory when a PAP device is prescribed. Polysonomography data contain total sleep time, wake after sleep onset, sleep efficiency, sleep latency, REM latency, sleep stages, arousal index, periodic limb movement index, and AHI, ODI (3%), average and minimum oxygen saturation levels, time spent below 90% oxygen saturation, and heart rate as well as the distribution of the respiratory indices during supine/non-supine position and during the REM and non-REM sleep stages. Sleep stages as well as respiratory parameters are scored in accordance with the criteria of the AASM from 2012 [4]; apnea was defined as a reduction in airflow of at least 90% for at least 10 s, and hypopnea was defined as a reduction in airflow of at least 30% accompanied by at least a 3% desaturation in the preceding 30 s, and a reduction in chest wall movement and/or arousal. AHI is referred to as the average number of apneas and hypopneas per hour of sleep, and OSA is defined as an AHI of at least five events/h, and the severity of OSA is categorized as mild (AHI 5.0–14.9 events/h), moderate (AHI 15.0–29.9 events/h), or severe (AHI 30.0 events/h). Before the analysis of the primary and secondary outcomes, separate definitions of clusters and phenotypes will be carried out accordingly by the TURKAPNE scientific working-groups.

Follow-up data regarding treatment modality and compliance
In cases with PAP treatment, the values at the PAP-titration night, PAP modality (i.e., fixed PAP, automatic PAP, bi-level PAP, adaptive servoventilator), and the applied pressure levels will be documented. Compliance data will be downloaded from the devices at follow-ups in accordance with each sleep center’s clinical routines.

Statistical Analysis
Standard statistical analysis will be performed using the IBM Statistical Package for the Social sciences version 22.0 for Windows software (IBM SPSS Corp.; Armonk, NY, USA). For comparison between multiple groups, one-way analysis of variance will be applied for continuous variables and Pearson Chi-square test will be performed for percentages. For comparison between subgroups, posthoc Bonferroni analysis will be performed where equal variances are found, and Games Howell analysis will be used where there is no equal variance. Regression analysis will be used for determining the relationship between OSA phenotypes and the outcome variables. All odds ratios will be presented with their 95% confidence intervals. All statistical tests will be two-sided, and p-values less than 0.05 will be considered statistically significant. Specific power estimates will be performed for each protocol before data analysis and the publication of the results.

RESULTS
The first patient was recruited in October 2017. A total of 25 sleep centers are presently registered as participating centers, of which 19 have actively entered a minimum of 30 patients by May 31, 2018 as required for the present paper; 1911 patients were entered into the database by May 31, 2018. The distribution of the enrolled cases per participating center is illustrated in Figure 2.

DISCUSSION
Obstructive sleep apnea is a frequently occurring condition with serious adverse outcomes, and the management of these high-risk individuals is presently not optimal either globally or in Turkey. The primary aim of the TURKAPNE study is to generate a cross-sectional nationwide database for defining clinical and polysomnographic characteristics of the patients with OSA. When completed, the project will contribute to a better understanding of the health burden of OSA phenotypes and its association with the comorbidities and adverse outcomes, including traffic accidents in Turkey. The results may also contribute to a more personalized approach and better management of varying OSA phenotypes with concomitant disorders.

*TURKAPNE Study Group

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Medical Faculty of the Marmara University, Istanbul (approval no: 09.2016.311).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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