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Cohort Profile

Cohort Profile: Cooperative Health Research in the Region of Augsburg (KORA) 1984–2024

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Key Features

- The KORA study (Cooperative Health Research in the Region of Augsburg) is a German population-based prospective cohort study investigating risk factors, early detection, and prevention of chronic diseases. KORA focuses on cardiovascular disease, diabetes, mental health, health in old age, lung health, and the role of social determinants and environmental exposures.
- The KORA study recruited 17 602 adult participants aged 25–74 years in four baseline surveys conducted between 1984 and 2001 in the Region of Augsburg, Germany.
- It includes up to 40 years of active follow-up for the initial participants and is ongoing to date. In 2021, of the initial 17 602 participants, 6493 participants were deceased and 2000 participants were lost to follow-up.
- Besides morbidity and mortality follow-ups, repeated follow-up examinations were conducted in subpopulations with questionnaire-based risk factor and socio-economic assessments. Genetic and molecular phenotyping contributed to identifying the underlying genomic, epigenomic, transcriptomic, proteomic, and metabolomic signatures of non-communicable diseases. Furthermore, the study is enriched by detailed environmental data at the place of residence and the establishment of a unique air-pollution measurement station.
- Data and biosamples can be requested for research projects via the KORA.PASST use and access hub (<https://helmholtz-muenchen.managed-otrs.com/external>).

Why was the cohort set up?

The KORA (Cooperative Health Research in the Region of Augsburg) study is a prospective population-based adult cohort study in Germany. It started in 1984 as the MONICA Augsburg study site in the international World Health Organization MONItoring of trends and determinants in CARdiovascular disease (WHO MONICA) project [1] and was renamed KORA in 1996 [2]. The KORA study is financed by the Helmholtz Zentrum München—German Research Center for Environmental Health and third-party funding. The KORA study now includes up to 40 years of active follow-up for the initial participants and is ongoing to date.

The overarching aims are health research and its translation into healthcare, improvement in prevention, diagnostics, and therapy, as well as policy advice. The scientific scope built on the cardiovascular focus of the MONICA project and extended to other non-communicable diseases, in particular type 2 diabetes, lung diseases, and mental health, and included several assessments of healthy ageing.

Who is in the cohort?

The KORA study has four independent cross-sectional baseline surveys, called S1 to S4. The study area covers the City of Augsburg and the two bordering districts of Augsburg and

Aichach-Friedberg (Fig. 1). Participants were identified based on age- and sex-stratified samples randomly drawn from the resident registration offices within the study area [1]. Specifically, samples were drawn in a two-stage procedure: first, the City of Augsburg and 16 communities from the adjacent districts were selected by cluster sampling and, second, stratified random sampling was performed within each community.

Inclusion criteria were being 25–74 years of age (25–64 years in S1), having the main place of residence in the study area, and being of German nationality [2]. Participants were excluded if they were lost to follow-up in the time interval between sampling and examination due to movement out of the study area, errors in the population register, death, or confinement in an institution.

In total, 18 079 participants took part in the four baseline surveys (Table 1 and Fig. 2). The number of participants was as follows: $N=4022$ (overall response: 79.3%) in S1, $N=4940$ (76.9%) in S2, $N=4856$ (74.9%) in S3, and $N=4261$ (66.8%) in S4. The overall response is defined as the proportion of participants out of all eligible participants (i.e. sampled persons excluding sample losses). The response did not differ between men and women, but increased per 10-year age groups, except for the oldest group in all surveys. In S4, 49% of the final non-responders completed a short questionnaire. They reported worse subjective health and a higher prevalence of myocardial infarction (MI) and diabetes [3]. The follow-up studies showed that there was duplicate

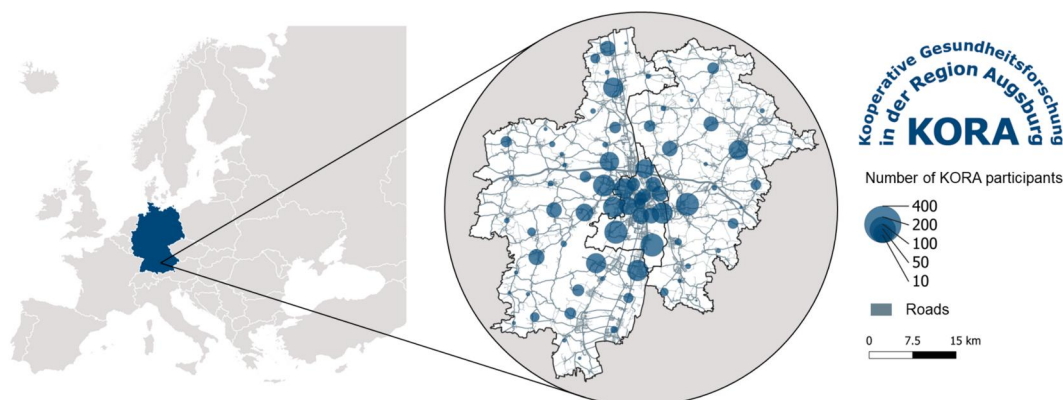


Figure 1. KORA study area in the Region of Augsburg. The number of KORA participants in 2021 is shown per postcode (positioned centrally). © GeoBasis-DE/BKG (2020) and © Deutsche Post Direkt GmbH.

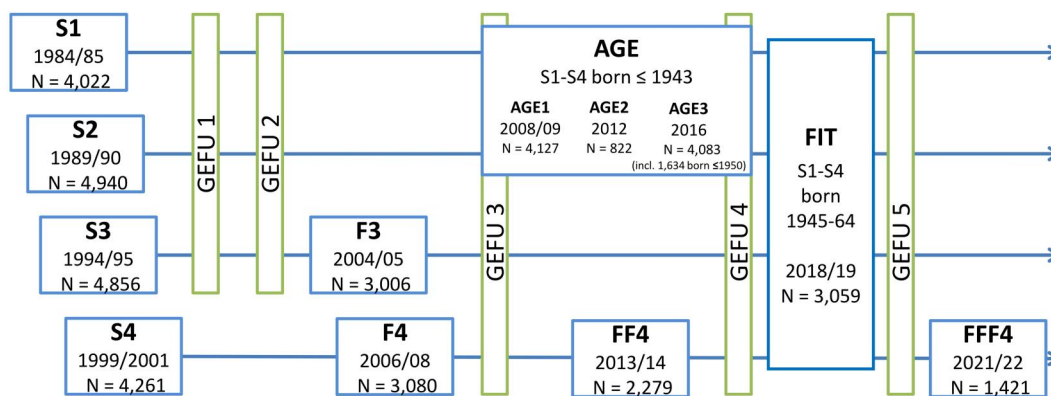


Figure 2. KORA study overview. The KORA study has four independent cross-sectional baseline surveys, called S1 to S4. The entire baseline surveys S3 and S4 were followed up in F3 and F4/FF4/FFF4, respectively. In addition, selected birth years from surveys S1–S4 were followed up with a specific scientific focus: AGE (participants born in or before 1943) on health in old age and FIT (participants born in 1945–1964) on fitness in older adults. The AGE study consisted of a telephone interview to all KORA participants born in or before 1943 and a medical examination of an age- and sex-stratified subsample. In the follow-up AGE3 in 2016, S1–S4 participants born in or before 1950 were added to the AGE cohort for comparison with the 2008/2009 sample. General health follow-up (GEFU) mailings on chronic disease status were conducted five times.

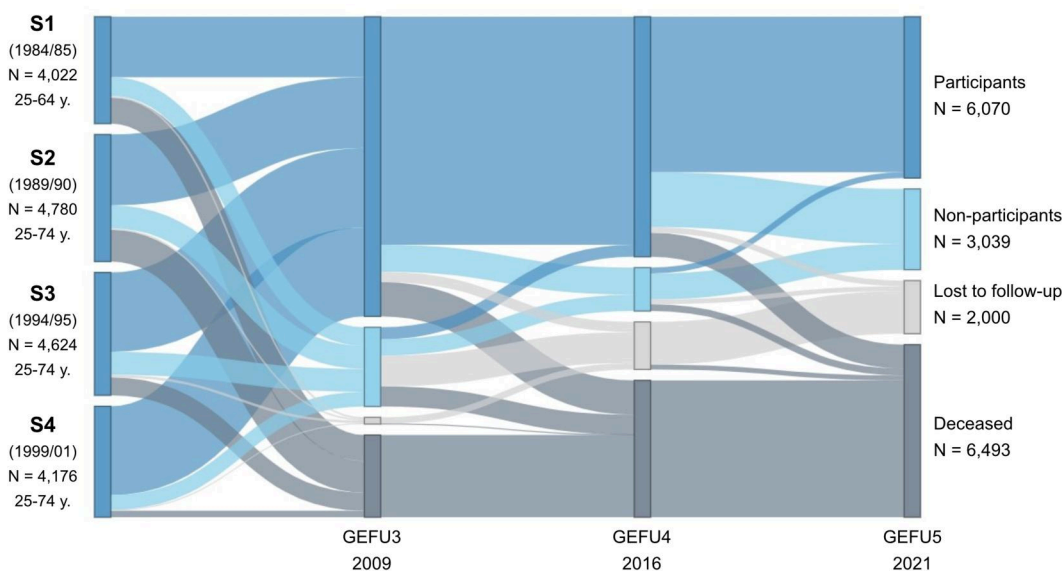


Figure 3. KORA study attrition from the four cross-sectional baseline surveys S1–S4 to the general health follow-up mailings (GEFU) in 2009, 2016, and 2021. Due to duplicate participation, the numbers of participants differ between Table 1 and Fig. 3.

participation. In total, $N = 17\,602$ unique individuals participated in the study excluding 477 duplicate participants.

How often have they been followed up?

The participants were followed up by using a combination of repeated examinations, postal and telephone questionnaires, and mortality follow-ups, building upon the MONICA approach. Figure 2 provides an overview of the major data-collection efforts within the cohort.

Follow-up examinations of entire baseline surveys (F3 and F4/FF4/FFF4) as well as cohorts defined by selected birth years were conducted (AGE, FIT) with a specific scientific focus. Some of these projects, such as the AGE or the Magnetic Resonance Imaging (MRI) study, are described in detail elsewhere [4, 5].

Vital status is checked at regular intervals through the population registries inside and outside the study area and, in recent years, by requests from the civil register ‘Anstalt für

Kommunale Datenverarbeitung in Bayern’ (<https://www.zemaonline.de>).

Morbidity and mortality were followed up by mailing general health follow-up (GEFU) questionnaires to all participants. There were five waves of GEFU questionnaire mailings, collecting disease incidence and mortality information until 2021.

Of the initial 17 602 unique participants, at the time of the GEFU5 follow-up in 2021, 6493 participants were deceased and 2000 participants were lost to follow-up (Fig. 3). The lost-to-follow-up group included participants who had moved out of the study region or out of Germany, or who had withdrawn consent to be re-contacted or to be part of the study. Table 1 shows the sex and age distributions at the baseline surveys and the follow-ups. Supplementary Table S1 illustrates the differences between those who died or were lost to follow-up and those who remained in the cohort until 2021. Over the 40-year period, willingness to participate in examinations remained high, but decreased from 79.6% to

53.8% for the examinations and from 82.3% to 66.6% for the questionnaire-based follow-ups (Table 1).

What has been measured?

Examination and self-reported data

A comprehensive list of the study methods of all major KORA studies are listed in the [Supplementary Tables S2 and S3](#). Briefly, data collection in the baseline examinations S1–S3 followed the core MONICA protocols and included anthropometric measures of waist and hip circumference, blood pressure, resting electrocardiogram, and medication use in the past 7 days, and a face-to-face interview on socio-demographic and -economic status; alcohol-consumption recall; cigarette smoking; leisure-time physical activity; sleep quality and duration; food-frequency questionnaire; self-rated health; self-reported chronic diseases such as MI, stroke, and diabetes mellitus and their family history; pregnancy and menopause; somatic complaints; type A personality; social support; and healthcare utilization. In S4, an oral glucose tolerance test for those aged 55–74 years was added. In addition, accelerometry, Ankle-Brachial Index, allergies, bioimpedance, 5-min 12-lead resting and 24-h Holter electrocardiogram, lung function, myopia, neuropathy, skin examinations, thyroid measurements, and many more were added in the follow-ups.

Morbidity and mortality

Validation of the survival status of non-responders was completed by contacting the municipal resident registration offices. Non-fatal and fatal clinical outcomes—especially diabetes mellitus, MI, and stroke—were validated by contacting physicians and/or reviewing hospital medical records and death certificates [6]. Death certificates were obtained from the district health departments in Bavaria and coded for the underlying causes of death according to the International Classification of Diseases (ICD-9 and, from 2000 onwards, additionally in ICD-10). Cardiovascular-related mortality consists of diseases of the circulatory system (ICD-9 codes 390–459, ICD-10 codes I00–I99) and sudden death with unknown cause (ICD-9 code 798, ICD-10 code R96). Cancer-related mortality consists of neoplasms (ICD-9 codes 140–208, ICD-10 codes C00–C97). Other disease-related mortality consists of the remaining causes of death, e.g. pneumonia (ICD-9 code 486, ICD-10 code J18), chronic bronchitis (ICD-9 code 491, ICD-10 codes J41, J42, J44), dementias (ICD-9 code 290, ICD-10 codes F03.90, F05, F01.50, F01.51), and deaths from suicide (ICD-9 E950–E959, ICD-10 X60–X84).

Non-fatal and fatal MI events or coronary deaths were coded based on the myocardial infarction registry in Augsburg for events that occurred in the study area in the age range of 25–84 years (25–74 years until 2009) [7]. MI was initially defined according to the WHO MONICA protocol [1] and, since 2001, according to the European Society of Cardiology and American College of Cardiology criteria [8]. The linkage with the registry ceased in 2019 for technical and organizational reasons when it became part of the University Hospital Augsburg.

For events that were not recorded in the registry and since 2020 exclusively, the diagnostic classification was performed by using death certificates, clinical diagnoses from the general practitioner's notes, or hospital discharge letters. Non-fatal stroke and diabetes morbidity was validated by physicians

who examined the clinical diagnoses from general practitioners' notes or hospital discharge letters.

Environmental data

Routine monitoring data of daily air-pollution concentrations and weather parameters are available through the services of the Bavarian Environment Agency or the German Weather Service. Since 2004, an aerosol measurement station has continuously monitored particulate matter including ultrafine particles and particle-size distributions [9].

In recent years, modelling of the spatial distribution of environmental factors has included air pollution, air temperature, relative humidity, noise, green space, as well as socioeconomic neighbourhood data. Geocoded residential addresses of the study participants are linked with the environmental factors and assigned to each participant.

Biosamples and omics

Standardized biosamples such as blood, serum, plasma, and urine were collected in almost all of the KORA studies ([Supplementary Table S4](#)). All samples were processed and aliquoted according to Standard Operating Procedures (SOPs) and stored at -80°C before being transported to the Biobank at Helmholtz Munich (<https://www.bbmri.de/ueber-german-biobank-alliance/muenchen-hmgu>). The biobank is certified according to DIN EN ISO 9001:2015. Depending on the study designs and research questions, participants were either non-fasting (S1–S3, S4 for the 25- to 54-year-olds, F3, AGE) or fasting (all other examinations) ([Supplementary Table S4](#)). Serum chemistry and blood counts were determined on the day of the examination at a hospital laboratory and additional parameters were measured from frozen material later for specific scientific questions. Omics measurements such as genomic, epigenomic, transcriptomic, proteomic, and metabolomic profiling and other molecular phenotyping as well as microbiome analyses from multiple sampling sites including stool, saliva, skin, and others have been performed ([Supplementary Table S5](#)).

Quality assurance and data management

Quality assurance and data management were implemented as part of the MONICA project and continuously adapted to the needs of the study. A pilot study was conducted before each examination to test novel procedures and timing. All project staff were trained to adhere to SOPs and quality-assurance measures were implemented. External audits at the KORA study centre were conducted for all examinations except FFF4.

What has it found?

Data from the KORA study have been used in >2200 publications (<https://www.helmholtz-munich.de/en/epi/publications/kora>). These have been published by KORA scientists and contributed to national and international consortia such as BiomarCARE, CARDIoGRAMplusC4D, CHARGE, DeTecT2D, DIAB-CORE, DIAGRAM, DIAMANTE, DigiMed Bayern, DIRECT, ENGAGE, ELAPSE, ESCAPE, EXPANSE, EXHAUSTION, GCVRC, GESA, GIANT, GLGC, HaemGen, IDP-Work, MAGIC, METASTROKE, MONICA, MolPAGE, MORGAM, NCDRisk, NGFN, SpiroMeta, STAGE, and SUMMIT. Some results are highlighted in [Fig. 4](#) and [Supplementary Table S6](#).

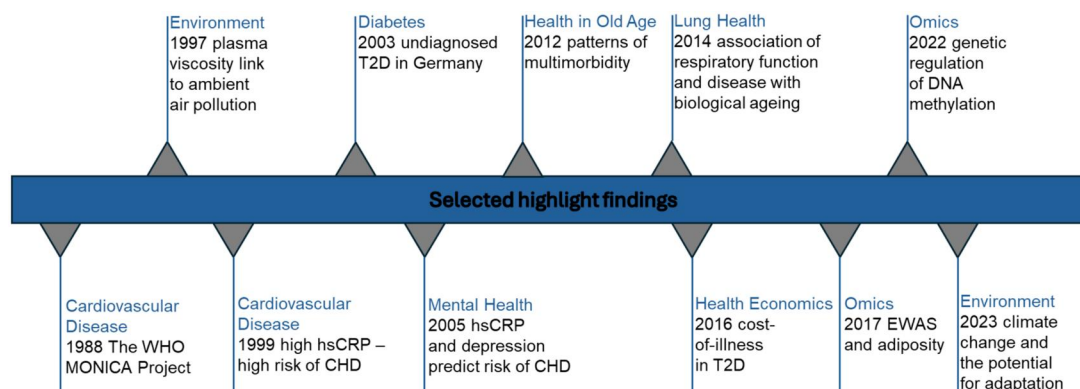


Figure 4. Selected KORA highlight publications. CHD, coronary heart disease; DNA, deoxyribonucleic acid; EWAS, Epigenome-Wide Association Study; hsCRP, high sensitive C-reactive protein; T2D, type 2 diabetes; WHO MONICA Project, World Health Organization MONItoring of trends and determinants in CArdiovascular disease Project. For more details, see also [Supplementary Table S6](#).

Cardiovascular diseases

The KORA study contributed significantly to the identification of novel biomarkers that improved risk prediction for cardiovascular events. Early work on high sensitive C-reactive protein (hsCRP) highlighted the strong positive association between increased levels of hsCRP and the risk of coronary heart disease [10]. More recently, it contributed to the development of the SCORE2 (Systematic Coronary Risk Evaluation 2) algorithm for the current risk prediction of cardiovascular disease in Europe [11] and the European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice [12].

Diabetes

The S4 study was the first population-based study in Germany to include an oral glucose tolerance test, revealing that ~40% of the study population aged 55–74 years had impaired glucose metabolism or diabetes, with half of the cases undiagnosed [13]. KORA contributed to the establishment of subclinical inflammation as a risk marker for type 2 diabetes [14] and identified novel predictors of type 2 diabetes using plasma proteomics [15]. A very fruitful clinical collaboration project was the MRI study on the subclinical disease burden of type 2 diabetes [4], with 65 publications to date (PubMed® search 14 October 2024).

Environment

Data from an air-pollution episode in the KORA study area in 1985 provided the first evidence of a systemic inflammatory response to ambient air pollution in the general population [16]. Advanced comprehensive molecular phenotyping in KORA allowed the impact of air pollution on DNA methylation to be assessed [17]. In the last decade, research on the health impact of climate change and the potential for adaptation was added [18].

Mental health

KORA investigated the prognostic influence of psychosocial stress on the incidence of cardiometabolic and other chronic diseases, focusing on underlying psycho–neuro–immunological mechanisms. For example, it was demonstrated that the combined effect of hsCRP and depressed mood was a far more powerful predictor of cardiovascular disease in initially healthy men than hsCRP alone [19]. Later work showed that

epigenomic upregulation due to psychosocial stress was associated with inflammation and cardiovascular risk [20].

Health in old age

Since 2008, the determinants and consequences of multimorbidity and frailty in older adults have been investigated in the AGE study to elucidate the reasons for successful ageing in the general population [21, 22]. Additionally, functioning and disability, falls, sarcopenia or muscle parameters, sarcopenic obesity, health-related quality of life, and mortality were analysed.

Lung health

Respiratory health and lung-function indices were introduced in F4 and used to establish reference values up to advanced age for spirometry [23] and impulse oscillometry [24]. Different and refined new approaches for the diagnosis and interpretation of respiratory impairment and disease, particularly in advanced age, were evaluated regarding their implications for clinical practice [25].

Omics

The KORA-gen platform was established to support genetic research in 2005 and multiple levels of omics data with repeated measurements are available today. It led to the world's first genome-wide association study (GWAS) of metabolite profiles [26] and is one of the most frequently contributing cohorts to GWASs worldwide [27]. DNA methylation signatures were found to be associated with adiposity and metabolic diseases [28] and the genetic regulation of DNA methylation was investigated [29]. Metabolomics data were employed for improved diabetes and MI risk prediction [30, 31].

Social determinants and health economics

The role of socio-economic differences in life expectancy, the effects of the implementation of new health policies such as German Disease Management Programs, and the cost of illness for relevant chronic diseases such as diabetes [32–34] are examples of how KORA has contributed to health economics research. Lately, it has contributed to the empirical basis on which to evaluate the potential role of societal interventions such as a sugar tax [35].

What are the main strengths and weaknesses?

KORA exemplifies how powerful population-based research can be if sustained over decades and enlarged in its breadth and depth. The main avenues were as follows. First, disease-specific as well as joint underlying pathways were investigated by the expansion from cardiovascular to metabolic and lung diseases, mental health, and age-related conditions, jointly with clinical partners. Second, the formation of the KORA-gen platform and collaboration with human geneticists, clinical collaborators and bioinformaticians, and international consortia allowed novel insights into the genetic determinants of non-communicable diseases. These research avenues were further expanded into pioneering work on metabolomics, epigenomics, and proteomics. Third, the focus on environmental determinants of disease led to groundbreaking work on the role of ambient air pollution and continues to date with a focus on the urban exposome and the role of climate change. Fourth, repeated examinations allowed the detection of early signs of non-communicable diseases. Finally, it is important to highlight that well-established cohorts never operate in isolation, are pillars for international collaboration, capture regional and national specifics, and form the basis for informed and causal assessments to preserve the health of current and future generations.

However, the KORA study is now a mature cohort study and is not representative of the general population in Germany. Through extensive recruitment efforts at baseline, a high response rate and thus reduced bias were achieved. However, the follow-up studies suffer from declining participation, especially among the less healthy participants [3], like other cohort studies. Ways to reduce bias are long-term cohort management [36] and the use of data acquisition via secondary data linkage such as mortality follow-ups together with state-of-the-art non-responder analysis.

Can I get hold of the data? Where can I find out more?

Data and biosamples can be requested for research projects via the KORA.PASST use and access hub (<https://helmholtz-muenchen.managed-otrs.com/external>). After registration, the data dictionaries as well as the KORA General Terms and Conditions are accessible. The KORA Board is responsible for review and approval of the requests. The rights of study participants, adherence to Good Scientific Practice, and the goals of the KORA study guide the decision. The European General Data Protection Regulation applies to all applicants.

Ethics approval

The KORA study was performed in line with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants at baseline as well as at each data-collection effort. Study methods have been approved by the Ethics Committee of the Bavarian Chamber of Physicians for each study since 1998. Prior to that, all studies were approved by the local authorities and conducted in accordance with the data-protection regulations valid at the time. The ethics committee numbers of all major studies are listed in [Table 1](#).

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Author contributions

Concept and design: B.L., A.P. Acquisition of data: all authors. Writing: C.G., M.H., R.H., W.K., K.-H.L., I.R., A.S., A.S., H.S., B.T., M.W., R.W.-S., K.W. Review and editing: all authors. All authors have read and agreed to the published version of the manuscript.

Supplementary data

[Supplementary data](#) is available at *IJE* online.

Conflict of interest

None declared.

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Data availability

See ‘Can I get hold of the data?’ above.

Use of artificial intelligence (AI) tools

No artificial intelligence tools were used in this manuscript except <https://www.deeppl.com> to improve the readability and English grammar.

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