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# Age, sex, and setting in the etiology of stroke study (ASSESS): Study design and protocol

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ABSTRACT

*Rationale:* Stroke etiology and risk factors vary by age, sex, setting (hospital or community-based) and by region. Identifying these differences would improve our understanding of stroke etiology, diagnosis, and treatment.
*Aim:* The Age, Sex and Setting in the Etiology of Stroke Study (ASSESS) is a multicenter cohort study to assess differences in stroke etiology.
*Methods and design:* Data from all centers will be categorized according to age, sex, setting, stroke subtypes. Centers with extensive hospital- or community-based data regarding stroke from Argentina, Australia, Canada, India, Iran, Italy, Ghana, Nigeria, Thailand, the United Kingdom and the United States have agreed to participate so far.
*Study outcomes:* The primary outcome includes differences in stroke etiology in study centers. The secondary outcomes include stroke incidence, risk factors, preventive strategies, and short- and long-term outcomes.
*Conclusion:* ASSESS will enable comparisons of data from different regions to determine the age and sex distribution of the most common causes of stroke in each setting. This will help clinicians to tailor the assessment and treatment of stroke patients on the basis of their specific local characteristics. It will also empower stroke epidemiologists to design preventive measures by targeting the specific characteristics of each population.

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## 1. Introduction

Stroke is one of the most devastating worldwide neurological disorders [1]. Despite a significant decline in the incidence and mortality rates of stroke in high-income countries, stroke-associated disability is on the rise worldwide, particularly in low- and middle-income countries [2,3]. Epidemiological trends in stroke vary substantially across time, age strata, sex, socioeconomic status, and regions [4–7]. In addition, the aging world population is leading to growing demands on the healthcare system, and this is having an alarming global financial impact [4].

Despite the wide regional variation in stroke characteristics [5,6], only a few attempts have been made to collect and compare data from different countries or continents [7]. The Age, Sex, and Settings in the Etiology of Stroke Study (ASSESS) was designed as a multicenter study of stroke to systematically gather and monitor data from different countries using a highly flexible approach. We report the study design, rationale, and methods, and we invite researchers worldwide to join this collaborative initiative.

## 2. Methods and design

### 2.1. Study plan

ASSESS is a multicenter study, designed to compare regional variations in stroke characteristics (i.e., age, sex, etiology, risk factors, socioeconomic status, outcomes, quality of care). This is an ongoing research project which has started from January 2018 and we welcome collaboration from investigators with similar studies across different regions to ensure a more global representation of stroke. (Fig. 1).

### 2.2. Ethics

ASSESS has been approved by Ethic Committee of local Institute of all the centres. We anticipate that participating centres will share anonymized data, which will be secured in protected servers and will remain confidential in an encrypted and secured dataset (RedCap), according to the requirements of the Lawson Research Institute, London, ON, Canada. For each specific study, we will get a new approval for data sharing and data analysis.

### 2.3. Data management

All the stroke centres have accepted the methodology of the current study. Data from studies in all centers will be harmonized and categorized according to whether the study was hospital- or population-based. We have developed a baseline list of variables with their definitions to facilitate the process of data-sharing to researchers interested in collaborating (online Supplementary tables I-IX). We acknowledge that data across studies is not homogeneous and we do not expect other datasets to perfectly match the needs of this study.

### 2.4. Statistical analyses

ASSESS will have a flexible policy for data sharing and analysis. We can either analyze at the coordinating centre (London, ON, Canada) or we can receive the results after being analyzed at each participating center. Specific statistical methods will be chosen according to the needs of each report.

### 2.5. Further studies

We plan to investigate variations in stroke incidence, risk factors, quality of care (preventive strategies and acute stroke care), short- and long-term outcomes. We also invite researchers to propose reports addressing local, regional, global knowledge gaps about stroke. An international steering committee will be created with the purpose of analyzing research proposals and to guide future steps. We will also invite young investigators to lead specific research projects under the guidance of senior scientists at each centre.

### 2.6. Final reports

Collaborators will be considered as co-authors of every publication if they meet the definition of author by the International Committee of Medical Journal.

### 2.7. Results

As a first step, we plan to include data from three centers, community-based studies in Argentina, Australia, and Iran, followed by hospital-based studies from Australia, Canada, India, Italy, and Thailand, the United Kingdom and the United States (Fig. 2).

### 2.8. The program for the epidemiological evaluation of stroke in Tandil, Argentina (PrEViSTA)

PrEViSTA, is a prospective population-based study of first-ever stroke and transient ischemic attack (TIA) in Tandil, Argentina, South America. It was conducted between January 5, 2013, and April 30, 2015. Using several overlapping strategies, all cases of first-ever strokes were identified. Overall, 334 patients with FES were recognized and were followed for 12 months after their index stroke [8].

### 2.9. The north east Melbourne stroke incidence study (NEMESIS)

The NEMESIS is a large population-based study of stroke in Australia. The study was performed in two consecutive phases. In brief, from May 1, 1996 to April 30, 1997 in a defined area of northeast Melbourne (133,816 residents) all suspected cases with stroke were identified ($n$ = 353 individuals, with 281 being first-ever strokes) [9]. In the second phase (between May 1, 1997, and April 30, 1999) and

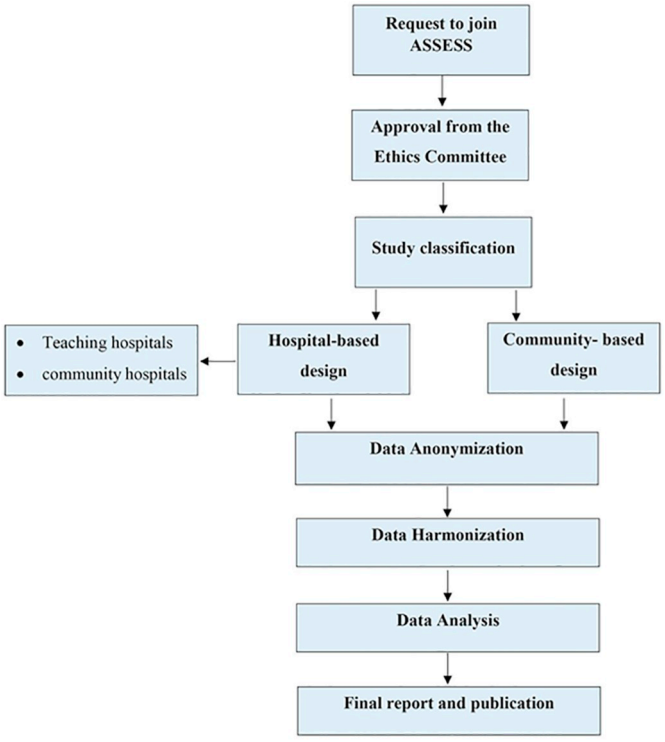


**Fig. 1.** Study design and plan to pool data from different countries.

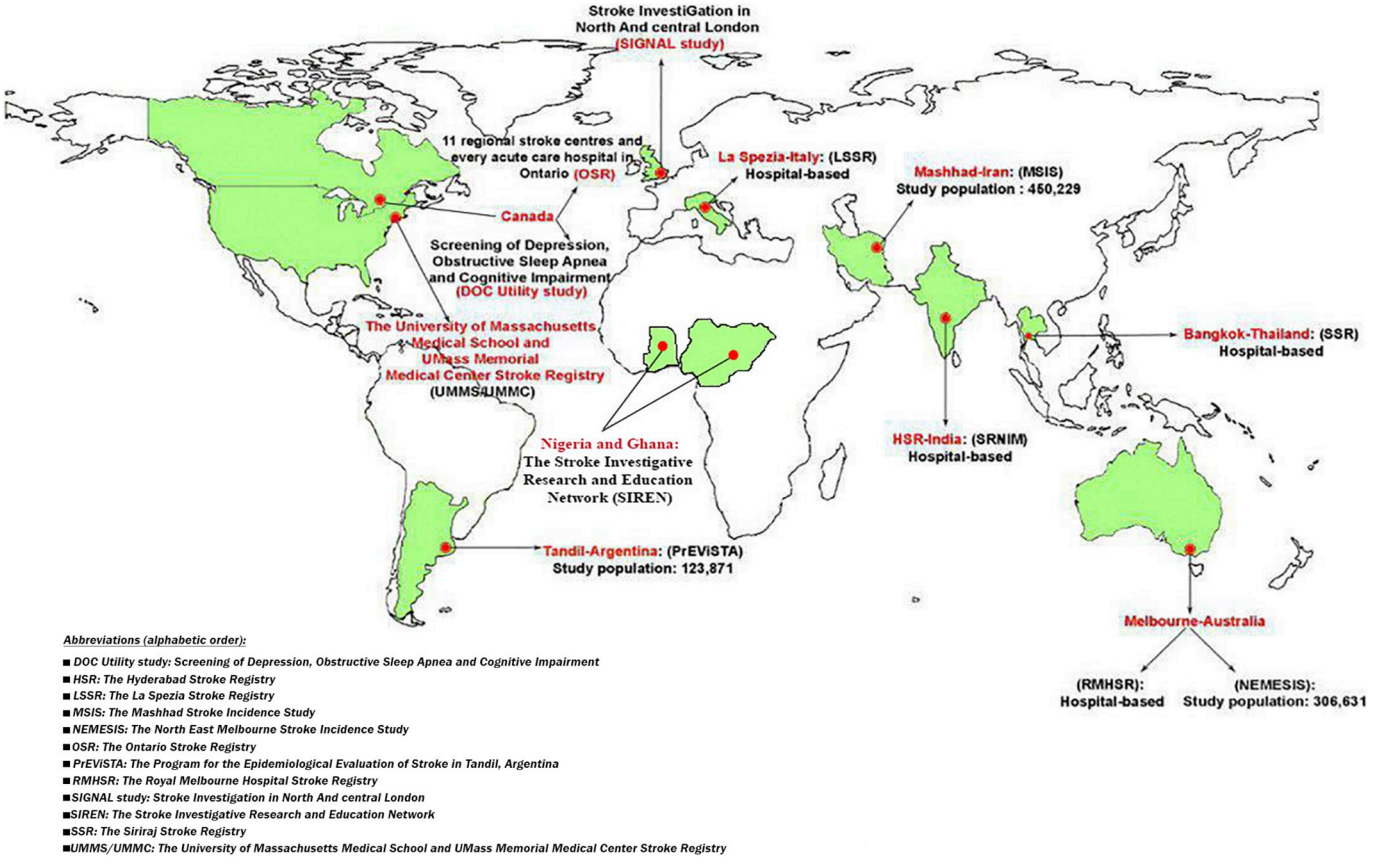


**Fig. 2.** ASSESS centers: Current collaborative centers in ASSESS.

after the expansion of the catchment areas to 22 postcodes (population 306,631), 1035 patients with first-ever stroke were recruited [10]. Patients were followed for 10 years after the index stroke.

### 2.10. The Royal Melbourne Hospital stroke registry

The Royal Melbourne Hospital is a major public teaching hospital in metropolitan Melbourne, Australia. The stroke unit treats approximately 800 patients per year with ischemic or hemorrhagic stroke, including approximately 100 intravenous thrombolysis cases. The hospital is also a 24–7 state-wide referral centre for endovascular thrombectomy for the state of Victoria (population 6 million), and performs approximately 200 endovascular thrombectomy cases per year. A prospective stroke clinical database has been collected since 2001.

### 2.11. The Ontario stroke registry

The Ontario Stroke Registry (OSR) comprises data on all consecutive patients with acute stroke or TIA seen in the emergency department or admitted to any of 11 regional stroke centres in the province of Ontario, Canada, North America, as well on a population-based sample of patients with stroke/TIA seen at every acute care hospital across the province between 2003 and 2013. The registry, with a sample size of > 90,000, is housed at the Institute for Clinical Evaluative Sciences (ICES) where it is linked to population-based administrative databases using unique, encoded identifiers to provide indefinite follow up for mortality, readmissions, physicians services and other outcomes, as well as information on medication use, area of residence and other demographic variables.

### 2.12. The Hyderabad stroke registry

The Hyderabad Stroke Registry is an ongoing, prospective hospital-based observational project based in Nizam's Institute of Medical Sciences, Hyderabad, the capital city of Telangana, South India, designed to comprehensively evaluate and record clinical, radiological, laboratory and outcome data of consecutive patients with acute stroke [11]. Nizam's Institute of Medical Sciences is a major neurological centre and teaching hospital in the city of Hyderabad with a large catchment area for neurological disorders. Patients are referred by practicing physicians or can get registered themselves. The patient population is fairly representative of the disease pattern in this region.

### 2.13. The Mashhad stroke incidence study (MSIS)

The MSIS is a large prospective population-based stroke study in Mashhad, northeast Iran, Middle East. Between 21 November 2006 and 20 November 2007, using multiple overlapping sources and with help from almost 1000 community health volunteers, a door to door survey was performed in three distinct regions of Mashhad (population: 450,229). Both hospital (admission, outpatients) and non-hospital (death certificates, private clinics, specialist referrals and national datasets) sources were used to identify any potential cases with stroke. 684 patients with acute stroke (624 with first ever stroke) and were followed for the next 5 years after their index event [12,13].

### 2.14. The La Spezia stroke registry

The La Spezia Stroke Registry is an ongoing hospital-based survey in the Stroke Unit, Sant Andrea Hospital, a community hospital in La Spezia, Italy, Europe. La Spezia is a port city in Italy with a catchment

area of 225,000 residents. All information on patients with stroke admitted in this center has been recorded since January 2014.

### 2.15. The Siriraj stroke registry

The Siriraj Stroke Registry is a large prospective hospital-based study in the Siriraj Stroke Center, Siriraj Hospital Bangkok, Thailand, Southeast Asia. Overall, 2942 patients with acute stroke were registered between 2007 and 2010.

### 2.16. The university of Massachusetts medical school and UMass memorial medical Center stroke registry

The University of Massachusetts Medical School and UMass Memorial Medical Center Stroke Registry is an ongoing hospital-based survey in Worcester, Massachusetts, United States. Worcester County is in central Massachusetts and the university hospital serves a catchment area of over 800,000 residents. All information on patients with stroke have been collected since June 2017.

### 2.17. Screening of depression, obstructive sleep apnea and cognitive impairment (DOC utility study)

The "DOC Utility" study is a prospective study funded by the Canadian Institute of Health Research to assess the impact of Depression, Obstructive sleep apnea and Cognitive impairment (DOC) symptoms on long-term outcomes in patients from stroke prevention clinics. We are prospectively screening over 7000 people at baseline visits to clinics across 8 regional stroke prevention clinics in Ontario, Canada. The outcomes will be 1-year event rates of recurrent stroke, heart attack, admission to long-term or complex continuing care and death, as defined by population-based administrative health records.

### 2.18. Stroke investigation in north and central London (SIGNAL study)

The study is an ongoing clinical stroke registry in London, the United Kingdom incorporating detailed stroke phenotyping (including advanced early MRI) embedded into standard clinical care, with follow up for clinical events and functional status. Currently over 1000 patients have been included, and it is expected that over 1000 patients with stroke will be included annually over the next 5 years.

### 2.19. The stroke investigative research and education network (SIREN)

The Stroke Investigative Research and Education Network (SIREN) [14–17] has the largest population of Africans with stroke in a single study comprising about 4000 cases and 4000 controls from many sites in Ghana and Nigeria, accurately phenotyped with state-of-the-art tools (pictographic questionnaire for stroke-free status for controls, and AIM-on –Clear Canvas Stroke phenotyping Software tool for cases) [18]. Subjects are comprehensively evaluated with a set of traditional and novel socio-demographic, clinical, and biochemical. Furthermore, the controls, who are recruited from the same catchment population as the cases are matched for age, sex and ethnicity. SIREN is aimed at unravelling the genetic and environmental risk factors for stroke among Africans and has identified the dominant environmental risk factors for stroke on the continent. SIREN, which commenced in 2013 is part of the H3Africa consortium [14–17].

## 3. Discussion

ASSESS is an ongoing pooled data study that can provide important knowledge about the age, sex, and setting of stroke in different countries, narrowing down the etiological possibilities. This study can also provide the opportunity to assess major questions in stroke, from basic incidence/long-term outcome trends in different countries to preventive and therapeutic measures. Such data are important for both health policy makers, at national and international levels, and stroke epidemiologists. In this paper, we provide the study design and rationale, a summary of the current collaborators and how other centers could join us.

Highly dynamic and variable trends of major diseases in the world require large collaborative national/international studies. This major need in world health data is fulfilled partly by the Global Burden of Disease (GBD) study, providing important worldwide trends in several diseases including stroke [2]. However, the results of many countries are based not on data but on sophisticated estimations [3]. Other important studies include METACOHORTS (the study of vascular disease and its contribution to cognitive decline and neurodegeneration) [19], and Statistical Modeling of Aging and Risk of Transition Project (data collection and harmonization across 11 longitudinal cohort studies of aging, cognition, and dementia) [20]. However, to implement appropriate measures to address stroke incidence and outcomes worldwide, it is necessary to gather data from a range of low- to high-income country and different settings. Given the large number of individuals captured in our dataset, we have sufficient statistical power to determine rare exposures, such as differences in risk factors for people with stroke aged < 55 year or uncommon types of stroke such as venous thrombosis, formulate new study hypotheses and perform specific sub-group analyses.

Although systematic reviews and meta-analyses can be used to combine available data, these methods make it difficult to control for potential confounding factors and adjust information according to study design, data heterogeneity, data collection methods and definition of variables [21]. Publication bias is also a major limitation of such studies, leading to the overestimation of effect sizes [22]. These issues can be overcome by using pooled data from many sources, similar to the ASSESS data set, whereby the chance of publication bias is reduced, and definitions of variables can be unified across different data sets [23].

Our study has some limitations. In comparison to systematic review and meta-analysis, pooled data studies are more expensive and time-consuming. Confounding variables can only be adjusted for if they were collected originally [24]. However, having access to all available data can give us the ability to adjust data and control the source of heterogeneity and assess new hypotheses. While the strict inclusion/exclusion criteria in multicenter clinical trials provide a homogenous group of individuals for data analysis, they are usually limited to an unrepresentative sample of patients with stroke. The heterogeneity of population-based samples should not be seen as a weakness but should be utilized to better elucidate differing patterns of stroke between regions. As the collaboration evolves, we plan to standardize the definitions and harmonize data gathering and analyses. Finally, it is important to consider dynamic changes in stroke trends during the previous decades, in both low- and high-income regions. By collaborating with most recent studies, we can closely monitor such a dynamic trend.

In summary, we have initiated an ongoing collaboration to pool data from different countries. We welcome other researchers/groups from different settings to participate in this study by providing data, or by proposing projects of national or international interest. We anticipate that this project will yield results of importance to policy makers in different parts of worlds and will provide opportunities for international collaboration.

## Acknowledgments

ASSESS is a multicenter study. Although we have not named many colleagues from all collaborating centers, we are truly grateful to them as without their devotions the current study could not have been performed.

## Statement of ethics

The studies were approved by Ethic Committee of local Institute and informed consent was obtained from patients or the next of the kin.

## Disclosures statement

The authors have no conflicts of interest to declare.

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## Author's contributions

- Writing the paper, critical revision: Nawaf Yassi, Antonia Nucera, Yongchai Nilanont, Subhash Kaul, Moira K. Kapral, Mariano Coppola, Cecilia Bahit, Suvarna Alladi, Brian Silver, Richard H. Swartz, David Werring, Robert Simister.
- Writing the paper, critical revision, data analysis: Negar Morovatdar, Amin Amiri
- Study design, writing the paper, critical revision: Vladimir Hachinski, Jennifer L. Mandzia, Luciano A. Sposato, Amanda G. Thrift, Mahmoud Reza Azarpazhooh.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.02.024.

## References

[1] D. Mukherjee, C.G. Patil, Epidemiology and the global burden of stroke, World Neurosurg. 76 (2011) S85–S90.
[2] V.L. Feigin, M.H. Forouzanfar, R. Krishnamurthi, G.A. Mensah, M. Connor, D.A. Bennett, et al., Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010, Lancet 383 (2014) 245–254.
[3] V. Hachinski, M.R. Azarpazhooh, Stroke is a burdensome but preventable brain disorder, Lancet Neurol. 15 (2016) 892–893.
[4] A. Chan, Y. Saito, J.-M. Robine, International perspectives on summary measures of population health in an aging world, J. Aging Health 28 (2016) 1119–1123.
[5] C. Gandolfo, M. Conti, Stroke in young adults: epidemiology, Neurol. Sci. 24 (Suppl. 1) (2003) S1–S3.
[6] J. Medin, A. Nordlund, K. Ekberg, Swedish hospital discharge register. Increasing stroke incidence in Sweden between 1989 and 2000 among persons aged 30 to 65 years: evidence from the Swedish hospital discharge register, Stroke 35 (2004) 1047–1051.
[7] B. Stegmayr, K. Asplund, K. Kuulasmaa, A.M. Rajakangas, P. Thorvaldsen, J. Tuomilehto, Stroke incidence and mortality correlated to stroke risk factors in the WHO MONICA Project. An ecological study of 18 populations, Stroke 28 (1997) 1367–1374.
[8] M.C. Bahit, M.L. Coppola, P.M. Riccio, L.E. Cipriano, G.A. Roth, R.D. Lopes, et al., First-ever stroke and transient ischemic attack incidence and 30-day case-fatality rates in a population-based study in Argentina, Stroke 47 (2016) 1640–1642.
[9] A.G. Thrift, H.M. Dewey, R.A. Macdonell, J.J. McNeil, G.A. Donnan, Stroke incidence on the east coast of Australia: the North East Melbourne Stroke Incidence Study (NEMESIS), Stroke 31 (2000) 2087–2092.
[10] A.G. Thrift, H.M. Dewey, J.W. Sturm, V.K. Srikanth, A.K. Gilligan, S.L. Gall, et al., Incidence of stroke subtypes in the North East Melbourne Stroke Incidence Study (NEMESIS): differences between men and women, Neuroepidemiology 32 (2009) 11–18.
[11] S. Kaul, P. Sunitha, A. Suvarna, A.K. Meena, M. Uma, J.M. Reddy, Subtypes of ischemic stroke in a metropolitan city of south India (One year data from a hospital based stroke registry), Neurol. India 50 (Suppl) (2002) S8–14.
[12] M.R. Azarpazhooh, M.M. Etemadi, G.A. Donnan, N. Mokhber, M.R. Majdi, M. Ghayour-Mobarhan, et al., Excessive incidence of stroke in Iran: evidence from the Mashhad Stroke Incidence Study (MSIS), a population-based study of stroke in the Middle East, Stroke 41 (2010) e3–10.
[13] H. Saber, A.G. Thrift, M.K. Kapral, A. Shoamanesh, A. Amiri, M.T. Farzadfard, R. Behrouz, M.R. Azarpazhooh, Incidence, recurrence, and long-term survival of ischemic stroke subtypes: A population-based study in the Middle East, International Journal of Stroke 12 (2017) 835–843.
[14] A. Akpalu, F.S. Sarfo, B. Ovbiagele, R. Akinyemi, M. Gebregziabher, R. Obiako, et al., Phenotyping stroke in sub-Saharan Africa: Stroke Investigative Research and Education Network (SIREN) phenomics protocol, Neuroepidemiology 45 (2015) 73–82.
[15] K. Morris, Charles Rotimi: engaging Africa in human genomic research, Lancet 376 (2010) 1383.
[16] H3Africa Consortium, C. Rotimi, A. Abayomi, A. Abimiku, V.M. Adabayeri, C. Adebamowo, et al., Research capacity. Enabling the genomic revolution in, Africa Sci. 344 (2014) 1346–1348.
[17] C.N. Rotimi, L.B. Jorde, Ancestry and disease in the age of genomic medicine, New Engl. J. Med. 363 (2010) 1551–1558.
[18] M. Owolabi, G. Ogbole, R. Akinyemi, K. Salaam, O. Akpa, P. Mongkolwat, et al., Development and reliability of a user-friendly multicenter phenotyping application for hemorrhagic and ischemic stroke, J. Stroke Cerebrovasc. Dis. 26 (2017) 2662–2670.
[19] METACOHORTS Consortium, Electronic address: joanna.wardlaw@ed.ac.uk, METACOHORTS consortium. METACOHORTS for the study of vascular disease and its contribution to cognitive decline and neurodegeneration: An initiative of the joint programme for neurodegenerative disease research, Alzheimer's Dement 12 (2016) 1235–1249.
[20] E.L. Abner, F.A. Schmitt, P.T. Nelson, W. Lou, L. Wan, R. Gauriglia, et al., The statistical modeling of aging and risk of transition project: data collection and harmonization across 11 longitudinal Cohort studies of aging, cognition, and dementia, Obs. Stud. 1 (2015) 56–73.
[21] S. Shapiro, Meta-analysis/Shmeta-analysis, Am. J. Epidemiol. 140 (1994) 771–778.
[22] M. Blettner, W. Sauerbrei, B. Schlehofer, T. Scheuchenpflug, C. Friedenreich, Traditional reviews, meta-analyses and pooled analyses in epidemiology, Int. J. Epidemiol. 28 (1999) 1–9.
[23] Collaborative Group on Hormonal Factors in Breast Cancer, Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies, Lancet 347 (1996) 1713–1727.
[24] L.A. Stewart, M.K. Parmar, Meta-analysis of the literature or of individual patient data: is there a difference? Lancet 341 (1993) 418–422.