Twin Research for Everyone

From Biology to Health, Epigenetics, and Psychology

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ACADEMIC PRESS
An imprint of Elsevier
elsevier.com/books-and-journals

CHAPTER

Twin family registries worldwide

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3.1 Introduction

During the last 65 years, twin registries have contributed much to our knowledge about genetic and environmental influences on all aspects of human behavior, physical characteristics, and health. The establishment of twin registries, then and now, is driven by the realization that a large sample size is critical to study the genetic basis of complex, heterogeneous, and polygenic traits and diseases. While the first twin registries were established in Europe, we now have twin registries on six continents, exceeding more than 60 twin registries across 26 countries (see Fig. 3.1 and Table 3.1).

Many twin registries are not limited to twins but also actively recruit family members of twins, changing into twin family registries, thereby enhancing the analytic power and the potential to study the processes of intergenerational associations and differences. The sample sizes of these twin family registries differ greatly, from a few hundred to over 250,000 participants, covering all ages. Since 2002, the journal of the *International Society for Twin Studies* (*Twin Research and Human Genetics)* has periodically published special issues on twin family registries in the world.[1–4] Fig. 3.2 shows the increases in the total number of participants (twins and their family members) in twin registries from 2002 to 2019 special issues. Between 2002 and 2019, the number of participating twins and their families increased over four times. Although a few registries have discontinued their activities during this period, the overall growth is due to an increase in the number of participants within existing twin registries as well as the incorporation of new twin registries over the years.

Twin Research for Everyone. DOI: https://doi.org/10.1016/B978-0-12-821514-2.00009-X

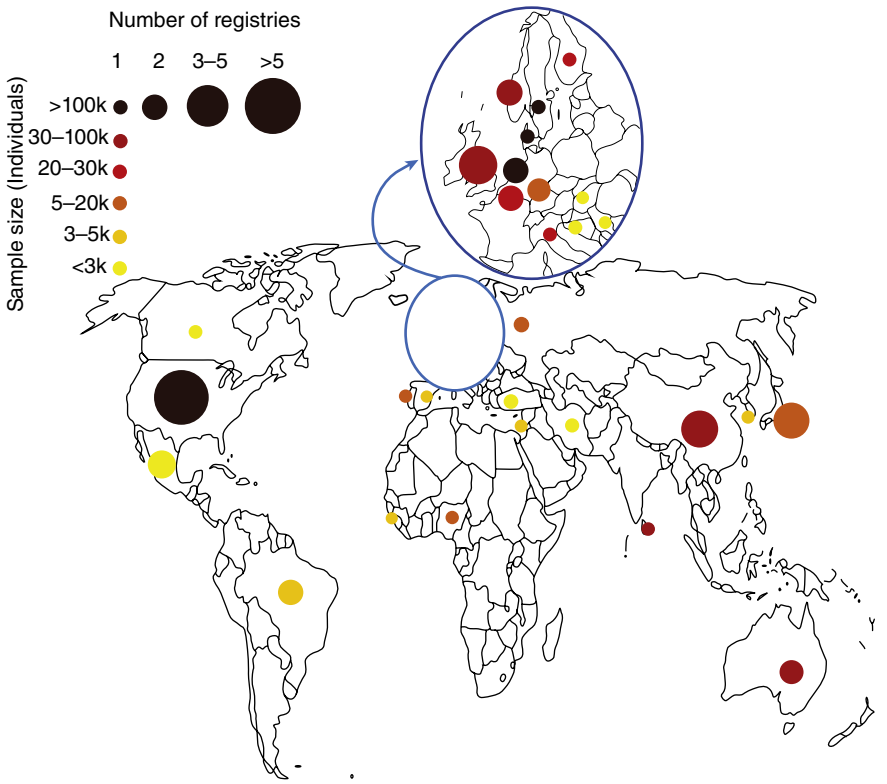

FIG. 3.1 Worldwide distribution of twin registries.

Table 3.1 provides an overview of twin registries across the world. In this chapter, we will briefly discuss registries per continent, touching upon the history, the variety of recruitment, and data collected. In this way, we hope to share with you the many opportunities for scientific study that twin registries continue to offer.

3.2 Twin family registries across the continents

3.2.1 Europe

The history of twin registries starts in Europe. The first official twin registry in the world was the Danish Twin Registry in 1954.[5,6] Originally established with the specific aim of studying cancer in a restricted cohort, its scope was broadened in time to many other aspects of health and lifestyle. This registry also grew to include a large percentage of the Danish twin population, recruited through a linkage with various registration systems such as church and conscription records, and national

Table 3.1 An overview of twin registries worldwide.

Country	Name of the registry (or running head)	Target region	Major recruitment methods	Total sample size	Subjects	Age in years	ZYG	Major phenotypes	DNA (biosample collection)	Reference/s and website
Australia	Twins Research Australia	National	Twin Pregnancy Booklet, internet, media, facebook, MBA	45,000 pairs	MZ, DZ, OSDZ	All ages	Q+ DNA	Health, psychological traits	Yes	42 www.twins.org.au
	Peri/Postnatal Epigenetic Twin Study (PETS)	Melbourne	Mothers recruited in pregnancy	250 pairs	MZ, DZ, OSDZ & their parents	10–12	DNA	Cardiometabolic, neuro-developmental	Yes	45 https://www.mcri.edu.au/peripostnatal-epigenetic-twins-study-pets
	Brisbane Longitudinal Twin Study	Brisbane & Queensland	Schools & media posting	7000	MZ, DZ, OSDZ & their siblings & parents	12–25	DNA	Melanoma, personality, cognitive abilities, psychiatric symptoms, neuroimaging, biochemistry	Yes	43 www.qtwin.org.au
	The Academic Development Study of Australian Twins	National	Twins registered with Twin Research Australia	4336	MZ, DZ, OSDZ, triplets, siblings	8–14	Q+ DNA	Reading, writing, spelling, grammar and numeracy, health	No	44 https://www.une.edu.au/about-une/faculty-of-medicine-and-health/school-of-psychology/research/the-australian-twin-study-of-the-naplan

(Continued)

Table 3.1 An overview of twin registries worldwide. *Continued*

Country	Name of the registry (or running head)	Target region	Major recruitment methods	Total sample size	Subjects	Age in years	ZYG	Major phenotypes	DNA (biosample collection)	Reference/s and website
Belgium	The East Flanders Prospective Twin Survey	East Flanders	Birth records	20,070	MZ, DZ, OSDZ & triplets	0–46	DNA, chor	Pre- perinatal influences on behavior and diseases	Yes	17 www.twins.be
	TwinssCan	East Flanders	East Flanders Prospective Twin Survey	1202	MZ, DZ, OSDZ & their families	15–35	Q+ DNA	Psychopathology	Yes	20
Brazil	University of Sao Paulo Twin Panel	National	University of Sao Paulo; media	4826	MZ, DZ, OSDZ, triplets+	All ages	Q+DNA	Psychological traits, anthropometric variables	Yes	71 https://www.paineluspdegemeos.com.br/
Canada	Quebec Newborn Twin Study	Quebec	Birth records	1324	MZ, DZ, OSDZ	0–19	DNA	Cognitive, behavioral, and social-emotional components of developmental health	Yes	36
China	Chinese National Twin Registry	National	Center for Disease Control, media	61,566	MZ, DZ, OSDZ, triplets+	All ages	Q+ DNA	Diseases, public health variables	Yes	50
	Beijing Twin Study	Beijing	Public schools	1387 pairs	MZ, DZ, OSDZ, triplets+	10–18	Q+ DNA	Psychopathology, psychological traits	Yes	51
	Guangzhou Twin Eye Study	Guangzhou	Guangzhou City Bureau of Statistics	1300 pairs	MZ, DZ, OSDZ, triplets+	7–30	DNA	Ocular data, anthropometry, cardiovascular risk factors	Yes	52

Country	Name of the registry (or running head)	Target region	Major recruitment methods	Total sample size	Subjects	Age in years	ZYG	Major phenotypes	DNA (biosample collection)	Reference/s and website
Denmark	Danish Twin Registry	National	Church records, Danish civil registration system, Conscription register, MBA	175,518	MZ, DZ, OSDZ, triplets+ & their families	10–100+	Q+DNA	Diseases, lifestyle/health-related behaviors, aging, cognitive and physical abilities, depression symptomatology, socio economic status	Yes	6 https://www.sdu.dk/en/Om_SDU/Institutter_centre/Ist_sundhedstjenesteforsk/Centre/DTR.aspx
England	Twins Early Development Study	National	Birth records	16,000 pairs	MZ, DZ, OSDZ	2–21	Q+DNA	Cognitive, emotional, and behavioral development	Yes	15 https://www.teds.ac.uk
	Children of the Twins Early Development Study	National	TEDS	554	children of TEDS	0–11	Q+DNA	Child psychopathology, temperament, cognitive development	No	16 https://www.teds.ac.uk/coteds
	TwinsUK	National	Media campaign	14,686	MZ, DZ, OSDZ	18–82	Q+DNA	Complex diseases and aging	Yes	12 http://twinsuk.ac.uk/
Finlanda	FinnTwin16	National	Central Population Register of Finland	30,527	MZ, DZ, OSDZ, triplets+ & their siblings, parents	16–35	Q+DNA	Substance use/dependence, lifestyle, mental & somatic health, psychosocial and socioeconomic traits	Yes	10 www.twinstudy.helsinki.fi

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Table 3.1 An overview of twin registries worldwide. *Continued*

Country	Name of the registry (or running head)	Target region	Major recruitment methods	Total sample size	Subjects	Age in years	ZYG	Major phenotypes	DNA (biosample collection)	Reference/s and website
Germany	German Twin Family Panel	National	Community registration office	4097 pairs & families	MZ,SSDZ & their siblings, parents,partners	5–25	Q+DNA	Social inequalities	Yes	19 https://www.twin-life.de/en
	Study of Personality Architecture and Dynamics	National	Media, twin clubs, city registration offices	1962	MZ,DZ, OSDZ, triplets+ & their spouses, children, parents	14–94	Q	Personality and related traits	No	80 www.speady.de/studies/?lang=en
Guinea-Bissau	Guinea-Bissau Twin Registry	Center & six suburban areas of Bissau	Hospital, population-based	3600	MZ, DZ, OSDZ & singleton controls	0 to young adults	Q+DNA	Metabolic disease, childhood twin mortality	Yes	66
Hungary	Hungarian Twin Registry	National (population based from 2021)	Media, previous databases, twin registries. From 2019: national database	1044 pairs	MZ, DZ, OSDZ & their families	All ages	Q	Health related variables & diseases (e.g., radiogenomics, musculoskeletal, cardiovascular and respiratory diseases, etc.), psychology, sociology etc.	Yes	ikrek.semmelweis.hu
Israel	Longitudinal Israeli Study of Twins	National	The Ministry of Interior	1657 families	MZ, DZ, OSDZ & their parents	3–15	Q+DNA	Prosocial behavior, empathy, temperament, values, parenting	Yes	60 https://soclabweb.wixsite.com/home/home

Country	Name of the registry (or running head)	Target region	Major recruitment methods	Total sample size	Subjects	Age in years	ZYG	Major phenotypes	DNA (biosample collection)	Reference/s and website
Italy	Italian Twin Registry	National	Municipality registry offices, maternity hospitals	29,000	MZ, DZ, OSDZ & their families	0–95	Q+DNA	Mental health, psychological traits, health related variables	Yes	22 https://scic.iss.it/gemelli/
Iran	Isfahan Twins Registry	National	Welfare agencies, public health homes, public & private nursing homes	1000	MZ, DZ, OSDZ, triplets+	All ages	Q+DNA, Nail, hair	Health and lifestyle related variables, behaviors and disease	Yes	61
Japan	Keio Twin Research Center	National	Government resident register	10,691 pairs	MZ, DZ, OSDZ	3–52	Q+DNA	Psychological traits, education related variables, mental health	Yes	54
	Osaka University Center for Twin Research	National	Media, posters	3000	MZ, DZ, OSDZ	All ages	DNA	Physical growth, health, dental phenotype	Yes	55
	West Japan Twins and Higher Order Multiple Births Registry	National	MBA, public health centers	12,041	MZ, DZ, OSDZ, triplets+	0–40	Q	Maternal and child health of families with multiples; physical growth	No	56

(Continued)

Table 3.1 An overview of twin registries worldwide. *Continued*

Country	Name of the registry (or running head)	Target region	Major recruitment methods	Total sample size	Subjects	Age in years	ZYG	Major phenotypes	DNA (biosample collection)	Reference/s and website
Korea, Republic	South Korean Twin Registry	National	Schools, maternity hospitals, MBA	4058	MZ, DZ, OSDZ	1–30	Q	Psychological traits, mental health	No	57
Mexico	Mexico Twin Registry (MexTR)	State of Jalisco	Public records of university students, MBA, maternity hospital	under plan	MZ,DZ, OSDZ	All ages	NA		under plan	72
	Mexican Twin Registry (TwinsMX)	National	Social media, public campaigns	145	MZ, DZ, OSDZ	18–60	Q	Somatic and mental health psychometrics, lifestyle	Yes	73 https://twins-mxofficial.unam.mx/
The Netherlands	Twin Longitudinal Investigation of Fetal Discordance	National	Hospital	plan to have 100 pairs+	Mono-chorionic twin pairs	Prenatal to 8	Chor	Fetal growth, cardiovascular diseases, neurodevelopmental impairment	Yes	18 www.twin-lifestudy.info
	The Netherlands Twin Register	National	City councils; commercial birth felicitation service; Dutch society of parents of multiples	255,785	MZ, DZ, OSDZ & their families	All ages	Q+DNA	Psychological variables, mental health, physical growth	Yes	8 http://www.tweelingenregister.org/.
Nigeria	Nigerian Twin and Sibling Registry	Lagos State, Abuja, FTC	Schools	5323	MZ, DZ, OSDZ, triplets, & singletons	10–21	DNA	Psychological traits, mental health	Yes	67

Country	Name of the registry (or running head)	Target region	Major recruitment methods	Total sample size	Subjects	Age in years	ZYG	Major phenotypes	DNA (biosample collection)	Reference/s and website
Norway	Oslo University Adolescent and Young Adult Twin Project	National	Birth records	4668 twin pairs & families	MZ, DZ, OSDZ & their families	12–22	Q+DNA	Psychological variables (personality), mental health	No	21
	Norwegian Twin Registry	National	Birth records, record linkages of national registries	32,664	MZ, DZ, OSDZ	28 and older	Q+DNA	Somatic & mental health	Yes	9
Portugal	Portuguese Healthy Family Study	National	Public schools	12,385	singleton children & their parents, sibling pairs	All ages	NA	Physical activity, body composition and physique, fitness & metabolic syndrome	No	24
Russia	Russian Twin School Registry	National	Public schools	5000	MZ, DZ, triplets	7-18	Q	Psychological characteristics, anthropometric measures, mental & somatic health	Yes	27 http://www.protwins.ru
Serbia	Serbian Twin Registry	National	Public campaigns, media, twin festival	1658	MZ, DZ, OSDZ, & their family members	All ages	Q+DNA	Psychological characteristics, anthropometric measures, mental & somatic health	Yes	81 http://www.blizanci.rs
Spain	Murcia Twin Registry	Regional (Murcia)	University, birth records	3545	MZ, DZ, OSDZ, triplets+	20+	Q+DNA	Health related variables	Yes	23 https://www.um.es/registro-gemelos/

(Continued)

Table 3.1 An overview of twin registries worldwide. *Continued*

Country	Name of the registry (or running head)	Target region	Major recruitment methods	Total sample size	Subjects	Age in years	ZYG	Major phenotypes	DNA (biosample collection)	Reference/s and website
Sri Lanka	Sri Lankan Twin Registry	National	Birth record, hospitals, media	34,280	MZ, DZ, OSDZ, singletons	All ages	Q	Mental disorders & metabolic syndrome	Yes	58 https://www.ird.lk/sltr/
Sweden	Swedish Twin Registry	National	Birth records	216,258	MZ, DZ, OSDZ	All ages	Q+DNA	Mental & somatic diseases, behavior	Yes	7 http://ki.se/en/research/the-swedish-twin-registry
USA	Arizona Twin Project	Arizona	Birth records	700	MZ, DZ, OSDZ	1–11	Q+DNA	Developmental psychopathology & somatic health	Yes	82
	Avera Twin Register	National	Media campaign	838	MZ, DZ, triplets+, siblings, & their parents	All ages	Q+DNA	Lifestyle, aging, diseases	Yes	83 www.avera.org/twin-register
	Boston University Twin Project	Massachusetts	Birth records	310 pairs	MZ, same-sex DZ	birth to age 5	DNA	Temperament and related behaviors	Yes	84
	CATSLife	Colorado	Adoption agencies	776	Mostly adoptees & their birth and adoptive parents	0–40	NA	Behavioral development, cognitive aging, health	Yes	85
	Colorado Twin Registry	Colorado	Schools, birth records	4500	MZ, DZ, OSDZ & their families	0–40	Q+DNA	Psychological traits (cognitive abilities, substance use and abuse, health etc.)	Yes	86 https://www.colorado.edu/ibg/research/human-research-studies/colorado-twin-registry

Country	Name of the registry (or running head)	Target region	Major recruitment methods	Total sample size	Subjects	Age in years	ZYG	Major phenotypes	DNA (biosample collection)	Reference/s and website
	Early Growth and Development Study	National	Adoption agencies	2456	Mostly adoptees & their birth and adoptive parents and siblings	0–20	NA	Temperament, behavior problems, mental health, obesity, achievement	Yes	87 https://www.egdstudy.org/
	Florida State Twin Registry	Florida	schools	5593	MZ, DZ, OSDZ, triplets+	11–22	Q	Reading development, school achievement, behaviors,	No	88
	Fullerton Virtual Twin Project	National	Media, multiple birth organizations, personal referrals	169	virtual twins	4.01–54.84	NA	Psychological traits	No	89
	Louisville Twin Study	Kentucky	LTS database	1770	MZ, DZ, triplets+, siblings, children of	All ages	Q+DNA	Psychological, physical growth	Yes	90
	Michigan State University Twin Registry	Michigan	Birth records, university	30,000	MZ, DZ	3–55	Q+DNA	Internalizing and externalizing psychopathology	Yes	91 https://msutwinstudies.com/
	Minnesota Center for Twin and Family Research	Minnesota	Birth records	23,199	MZ,DZ, adoptees	7 to old adults	Q+DNA	Substance use and related psychopathology	Yes	31 https://mctfr.psych.umn.edu/
	Mid-Atlantic Twin Registry of Virginia Commonwealth University	Virginia, North & South Carolina	Birth records, schools	54,042	MZ, DZ, triplets+ & their families	All ages	Q+DNA	Developmental psychopathology	Yes	34

(Continued)

Table 3.1 An overview of twin registries worldwide. *Continued*

Country	Name of the registry (or running head)	Target region	Major recruitment methods	Total sample size	Subjects	Age in years	ZYG	Major phenotypes	DNA (biosample collection)	Reference/s and website
	NAS-NRC Twin Registry & Duke Twin Study of Memory in Aging	National	Birth records linked with army records	31,848	male MZ & DZ	15–82	Q+DNA	Anthropometric, health and mortality, education and earnings	Yes	32
	National Project on Achievement in Twins	National	Schools	2514	MZ,DZ, OSDZ	4.25–14.25	Q	Reading development, school achievement, behaviors,	No	37 http://www.idcd-lab.com/natpat-twin-project.html
	Pennsylvania Longitudinal Study of Parents and Children	Pennsylva-nia state	Schools, birth records	2260	MZ, DZ, OSDZ, triplets+ & their parents	0–88	Q	Mental & somatic health, prosocial traits	No	92
	Project Talent Twin and Sibling Study	National	Schools	5003	MZ, DZ, OSDZ, triplets+ & their siblings	14–78	Q & photo	Cognition, personality, education, occupation, activities, health, aging	No	38 projecttalent.org
	Southern Illinois Twins/Triplets and Siblings Study	Illinois	Media, birth records	1175	MZ,DZ, OSDZ, triplets+, siblings	1–20	Q+DNA	Childhood aggression, parent-child interaction, emotional development	Yes	93 https://www.siumed.edu/playlab/twin-play-lab.
	Vietnam Era Twin Study of Aging	National	Army records	1230	male MZ, DZ	50–70	DNA	Cognitive and brain aging, Alzheimer's disease	Yes	35

Country	Name of the registry (or running head)	Target region	Major recruitment methods	Total sample size	Subjects	Age in years	ZYG	Major phenotypes	DNA (biosample collection)	Reference/s and website
	Washington State Twin Registry	Washington State	Department of licensing	9668 pairs	MZ,DZ, OSDZ	All ages	Q+DNA	A variety of somatic and mental health outcomes	Yes	94 ttps://wstwinregistry.org/
	Wisconsin Twin Project	Wisconsin	Birth records	5000 pairs	MZ, DZ, OSDZ	Prenatal to 24	Q+DNA	Temperament, affective neuroscience, developmental psychopathology, puberty	Yes	95 https://goldsmithtwins.waisman.wisc.edu/
Consortia	Collaborative Project of Development of Anthropometrical Measures in Twins (CODATwins)	24 countries	Twin registries in the participating countries	489,981	MZ, DZ, OSDZ	0 to about 90	Q+DNA	Height, BMI, education, smoking		79
	Interplay of Genes and Environment across Multiple Studies (IGEMS)	Australia, Denmark, Finland, Sweden, USA	Twin registries in the participating countries	76,233	MZ, DZ, OSDZ	14–103	Q+DNA	Dementia, mortality, physical, SES, & psychological functioning		76 https://dornsife.usc.edu/labs/igems/
	Nordic Twin Study on Cancer (NorTwinCan)	Denmark, Finland, Norway, & Sweden	Twin registries in the participating countries	315,413	MZ, DZ, OSDZ		Q+DNA	Cancer		75

Note. Numbers in "total sample size" refer to individual twins unless "pairs" is stated. ZYG, zygosity assessment methods; MZ, monozygotic twins, DZ, dizygotic twins; OSDZ, opposite-sex dizygotic twins; SSDZ, same-sex dizygotic twins; MBA, multiple birth association; Chor, chorionicity; Q, questionnaire method; NA, not applicable; Q+DNA= questionnaire supplemented by DNA testing; [a]Finland has two other twin family registries: see Rose et al.[96] for the FinnTwin12 cohort and Kaprio et al.[97] for the Older Finnish Twin Cohort. Table was adapted from Table 2 in Hur et al.[4], with permission.

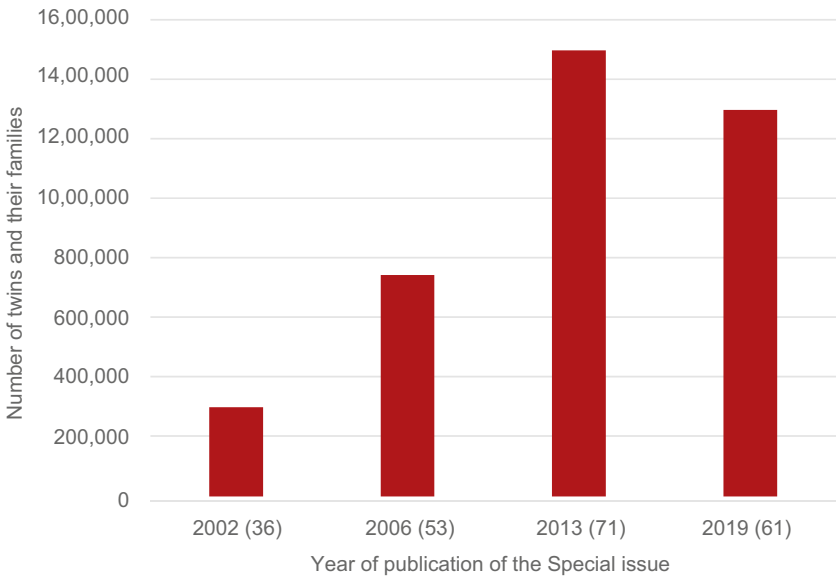

FIG. 3.2 Increases in the number of participants (twins and their families) reported in special issues of *Twin Research and Human Genetics* from 2002 to 2019. The number of twin registries in each special issue is in parenthesis.

health registries in Denmark. National twin registries in other European countries quickly followed, first primarily in the Nordic countries but later also in other parts of Europe. As evident from Table 3.1, Europe at the time of this chapter still contains the most twin registries across the continents, as well as the two largest registries in the world: the Swedish Twin Registry (STR)[7] and the Netherlands Twin Register (NTR),[8] both including more than 200,000 participants from all ages. While the STR has more information on the elderly, the NTR is unique in the large number of newborn twins it has followed across the lifespan from the late 1980s onwards. This allows for the study of the influence of genetic and environmental factors on many aspects of the development from early childhood into adulthood.

Though smaller in size than their neighbors, the two other Nordic twin registries, the Norwegian[9] and the Finnish Twin Registries,[10] are still very large and extensive in their data collection. As in most twin registries, general longitudinal surveys are sent out periodically while detailed phenotypic information may be obtained in specific projects, such as the volumes of fat and lean body mass via body scan, cholesterol, and glucose levels via blood samples, as well as the outcomes of cognitive tests and brain activity via electroencephalography (EEG) recordings. In addition, many cohorts collect genotypic and epigenetic data on their participants. Depending on the focus and costs, such information may be available for all those in the registry or for only a selected group. For instance, the Finnish Twin Registry obtained body scans and fat biopsies for a subset of monozygotic (MZ) twins discordant for obesity, allowing for more insight into the biological mechanisms associated with obesity.[11]

Many twin registries continuously expand the information they collect based on scientific developments. A good example of this is TwinsUK,[12] which recently collected stool samples from many of its participants, leading to the first publications on the heritability and molecular genetics of the microbiome.[13,14]

Twin registries may also develop in other ways. The Twins Early Development Study (TEDS)[15] was established in 1994 in the UK to study the emotional and cognitive development in young twins, but as the participants grew older and started their own families, the children of the TEDS participants led to a third separate registry.[16] Other twin registries have also started to follow the offspring of twins, but none made this such an explicit aim as the Children of the TEDS.[16]

There are three types of MZ twins based on the time of zygotic division: the dichorionic-diamniotic pairs (splitting before the 4th day after fertilization), the monochorionic-diamniotic pairs (splitting between the fourth and the seventh day after fertilization), and the monochorionic-monoamniotic pairs (splitting after the eighth day after fertilization).[17] As MC twins share a single placenta, they are frequently exposed to a vastly discordant prenatal environment due to complications. The TwinLIFE[18] identifies (at least) 100 monochorionic (MC) twin pairs born in Dutch hospitals, stores their biological samples at birth, and follows the twins from the prenatal period into childhood longitudinally. By studying intrapair differences in DNA methylation and future health development, the TwinLIFE can provide powerful insight into the effects of pre- and peri-natal environments on later health.

With also a large population registry in Belgium,[17] unique in its access to perinatal and placental information, and a recently established German registry with a focus on socioeconomic circumstances,[19] and additional smaller twin cohorts in Belgium and Norway focusing on psychopathology,[20,21] it is evident that Northern and Western Europe are well represented in twin registries. Fortunately, over the past years, twin registries have also been established in Southern Europe, and twin registries in Italy,[22] Spain,[23] and Portugal[24] with a strong focus on health and health-related behaviors, are rapidly increasing in numbers and data collection. More recently, the Hungarian Twin Registry was established which has a strong focus on health and disease but also collects psychosocial information on its participants.[25] Of interest is the Russian twin registry, which in part represents Europe but also reflects Asian cultures. The Russian Federation actually has a very long and rich history of twin studies with many prominent names and findings,[26] but a nationwide representative school-aged twin registry only developed over the last decade.[3,26] So far, the Russian School Twin Registry (RSTR) has recruited 5.000 twins from 7 to 17 years of age, of different ethnicities and culturally distinct populations, but it expects to include more than 100.000 school-aged twins to study the role of the interplay between genetic and environmental factors in the development of academic achievement.[27,28] Another twin registry located both in Europe and Asia is the Turkish Twin Study[29] which specifically focuses on the role of cultural differences in the etiology of health problems.

Hopefully, the expansion across the eastern and southern parts of Europe will continue, but it is certain that the European twin registries will continue to contribute much to our knowledge about genetic and environmental influences on behavior and health.

3.2.2 North America

Even though the history of modern twin studies in North America is younger than in Europe, during the last decades a vigorous tradition of twin research has developed in North America as demonstrated by a large number of twin cohorts. There are at least 25 independent twin cohorts in the United States and two twin cohorts in Canada (see Table 3.1). An early milestone for the twin studies in the United States was the establishment of the Minnesota Study of Twins Reared Apart (MISTRA) in 1979 which studied adult twins separated early in infancy and reared in different families.[30] This project has provided important contributions to our understanding of the role of genetic factors in the variation of psychological traits. The first studies published in the early 1980s were based on only a small number of reared-apart MZ pairs but still suggested that genetic factors play an important role in the variation of complex behavioral traits. However, the study on the heritability of IQ published in 1990 including data from over 100 reared-apart twin pairs or triplets clearly demonstrated the large influence of genetic differences on the individual variation in cognitive abilities.[30] In addition to MISTRA, there were several studies of twins raised together at the University of Minnesota, which were later integrated into the Minnesota Center for Twin and Family Research (MCTFR).[31] Although the main focus of the MCTFR is substance use and related psychopathology, it has investigated psychological adjustment, personality, cognitive ability, brain function, and other physiological traits longitudinally. However, the history of US twin studies goes further back in time, and actually the oldest systematically collected measures of twins are available from a study started in 1965.[32] This study made use of the military records collected in the past for US veterans. This resulted for example in height and BMI measurements in twins conducted in the early 1940s and thus allows estimating the heritability for traits obtained two decades earlier.[33]

Currently, the US twin registries include a wide variety of cohorts, each having own specific strengths. The largest cohort is the Mid-Atlantic Twin Registry[34] having a sample size of more than 50,000 twins, triplets, and their family members. Most of the North American cohorts are relatively small having less than 5000 and in many cohorts less than 1000 twin individuals or relatives. However, the smaller sample sizes compared to many European twin cohorts is in many cohorts compensated by intensive clinical measures often not available for bigger cohorts. For example, the Vietnam Era Twin Study of Aging includes detailed measures of brain based on neuroimaging as well as cognitive tests.[35]

North American cohorts often focus in their data collection on a specific state or another well-defined geographic area, such as Greater Montreal area of Quebec Newborn Twin Study.[36] However, there are a few exceptions in the US cohorts. Two US cohorts represent male war veterans: the National Academies of Science - National Research Council (NAS-NRC) twin registry[32] and the Vietnam Era Twin Study of Aging.[35] National school records have been used in sampling twins in the National Project on Achievement in Twins[37] as well as in the Project Talent Twin and Sibling Study.[38] Further, some cohorts were developed focusing on groups otherwise underrepresented in scientific research, such as the Carolina African American Twin

Study of Aging[39] and the Texas Twin Project,[40] which includes overrepresentation of ethnic minorities.

The number of traits collected in North American twin studies is vast, covering all aspects of human development, behavior, and health, although most studied topics have been psychological traits including cognitive development and school achievement. Psychopathology, especially, substance use/abuse (including tobacco and alcohol) and personality measures also received much attention. While traits related to physiology (with the exception of psychophysiological measures) and physical diseases have also been included in North American cohorts, these traits are less intensively studied than in European cohorts. This reflects the tradition in North America that twin research has been mainly linked to psychological research and many twin cohorts have been collected at departments of psychology. However, like European counterparts, many Northern American registries now also include genotypic and epigenetic information.

3.2.3 Australia

The origin of twin registries in Australia dates back to the 1970s when the first state registries were founded, which then received support from the National Health and Medical Research Council. The twinning rate in Australia is 16.2 per 1000 births, which is comparable to those in European countries.[41] The largest Australian national registry up to date, the Australian Twin Registry, now renamed as Twins Research Australia (TRA),[42] is located in Melbourne, Victoria, and enrolled more than 40,000 twin pairs and higher-order multiples of all ages over its 40-year history, representing approximately 20% of twin pairs in Australia. For the past decades, TRA has studied health and many diseases including cancers. While playing an active research role itself, TRA provides news and information to twin members and their families through its website, and promotes twin community forum to influence practice and policy on twins in Australia. TRA also supports twin researchers and prospective students from multiple disciplines by providing open access to its volunteer twin membership and training for statistical analyses for twin studies.

Another large Australian registry—Brisbane Longitudinal Twin Study (BLTS)—is located in Queensland at the South East coast and recruited around 5000 twins and siblings at 12 years old between 1992 and 2018.[43] Over the past years the BLTS contributed to the understanding of the role of genetic factors in melanoma risk (mole study), personality traits, psychiatric symptoms, and IQ; and conducted studies in the fields of neuroimaging, haematology, biochemistry, and ophthalmology. Several specialized registries in Australia covered specific topics. For example, the Academic Development Study of Australian Twins (ADSAT) longitudinally studied educational achievement in twin pairs, higher-order multiplies and siblings with literacy and numeracy testing in different grades.[44] The Peri/Postnatal Epigenetic Twins Study (PETS) recruited mothers of 250 twin pairs during pregnancy and have studied on genetic and intrauterine components of variation in the human neonatal epigenome, fetal programming, and early factors of later diseases.[45] Other registries include the Teeth

and Faces of Twins Registry[46] focusing on the study of genetic, epigenetic and environmental influences on dentofacial structures and oral health and the Australian Twin and Ophthalmic Traits Registry,[47] focusing on eye physiology and visual disorders.

Australian twin registries have played a prominent role in twin research and their researchers have made important contributions, especially in the development of methodology for causal inference, polygenic risk scores, integrative omics analysis, and combination of twin data with other kinds of data from different sources (such as geospatial and environmental data).

3.2.4 Asia and Middle East

Asians, especially East Asians, have the lowest natural twin birth rates in the world, with a rate of 4 to 6 pairs per thousand births.[48] Recently, however, due to the increased use of assisted reproductive technologies, twin birth rates have increased sharply across many East Asian countries, facilitating development of twin studies. Twin birth rates in Middle East remain poorly understood. However, a rate of 14.4 pairs per thousand birth has been reported recently.[49]

Large-scale, population-based twin registries are currently maintained in China, Japan, and South Korea in East Asia and Sri Lanka in South Asia. The Chinese National Twin Registry,[50] currently the largest twin register in Asia, recruits twins mainly through the Centers for Disease Control throughout the country, and focuses on disease and public health issues. In addition, two other regional registries are available to study psychopathology and ophthalmological traits in Chinese children and adolescents.[51,52] For example, the Guangzhou Twin Eye Study research team recently showed that within discordant MZ twin pairs, the more myopic twin was associated with performing more near-work activities than their co-twins, confirming environmental risk factors in myopia.[53]

Japan has currently three active registries: Keio Twin Research Center (KTRC),[54] Osaka University Center for Twin Research (Osaka Twin Registry),[55] and West Japan Twins and Higher Order Multiple Births Registry (West Japan Registry).[56] These registries use different ascertainment schemes and study somewhat different phenotypes. While the KTRC focuses on psychological and education-related traits, the Osaka Twin Registry and the West Japan registry concentrates on health issues and physical growth. The West Japan registry is unique in that they have a very large number of higher-order multiples and can serve as a valuable resource to study specific concerns regarding higher-order multiples.

The South Korean Twin Registry (SKTR)[57] is a nationwide volunteer registry founded in 2001. It includes twins from preschool to young adulthood age, with the aim of studying genetic and environmental influences and their interplays in psychological and mental health traits in South Koreans. The SKR has demonstrated that heritability for personality traits from children to young adults and symptoms of various types of psychopathology are comparable to those found in many western twin studies.[57]

A nationwide population-based twin registry was established in Sri Lanka in 1997 to study genetic and environmental etiologies of mental disorders and metabolic

syndrome in low- and middle-income countries.[58] The Sri Lankan Twin Registry currently includes over 30,000 twins and singletons of all ages. The registry team recently found that while the levels of risk factors for the metabolic syndrome in Sri Lankan twins were similar to those found in western samples, the prevalence of depressive/anxiety symptoms was lower in Sri Lankans than in Westerners.[59]

In the Middle East there are currently two twin registries. The Longitudinal Israeli Study of Twins (LIST)[60] and the Isfahan Twin Registry (ITR) in Iran.[61] The LIST identified twins born in Israel in 2004 and 2005, and has studied prosocial behavior and related traits longitudinally since 2007. Although mail surveys have been conducted regularly, experimental and observational data of social behavior have been collected longitudinally, which are major strengths of the LIST. Additionally, the Isfahan Twin Registry (ITR) was launched in Iran in 2017 to study (epi)genetic causes of diseases, especially cancer, diabetes, and cardiovascular diseases in Iranians. The registry now includes more than 1000 participants and collects biological samples, medical records, and questionnaire data from twins and multiples to establish a biobank.

3.2.5 Africa

Africa has the highest twin birth rates in the world,[48] with rates varying from 20 pairs to 49 pairs per thousand births.[62,63] The reasons for these high rates include a higher level of follicle-stimulating hormone in African women as compared to women of other ethnic origins,[64] diet, and high parity.[65] Despite these high twin birth rates, few twin studies have been conducted in Africa due to lack of research infrastructure and facilities, political instability, and high rates of illiteracy. Only two twin registries are currently established on the African continent: the Guinea-Bissau Twin Registry (GBTR)[66] and the Nigerian Twin and Sibling Registry (NTSR).[67]

The GBTR was founded in Bissau in 2009. In collaboration with the Bandim Health Project that maintains the health and demographic surveillance system (HDSS) in Bissau, the registry has collected medical data and biological materials from newborns to 30 years of age ($N > 3600$) since its inception. The GBTR aims to investigate risk factors for newborn twin mortality and the etiology of metabolic disorders specific to African populations. A recent GBTR study reported higher body fat percentage and glucose levels in both the fasting and postprandial state for twins compared to singletons, which the researchers suggest may be due to suboptimal nutrition during twin pregnancy.[68]

The NTSR was initiated in 2010 to study genetic and environmental influences and their interplays for psychological and mental health traits in Nigerian children and adolescents. Because the birth registration system is not well developed in Nigeria, twins in the NTSR are identified through public schools. As of 2019, over 5000 twins and their families have been registered with the NTSR.[67] Even though living conditions in sub-Saharan Africa are vastly different from those in many developed countries, the findings from the NTSR samples to date suggest that genetic and environmental influences on cognitive abilities, prosocial behavior, religious attendance, and family environments are largely similar to those reported in twin samples from developed countries.[67]

3.2.6 Latin America and the Caribbean

The history of twin registries in Latin America and the Caribbean (LAC) is still to be written, and the absence of data has left out Central and South American populations as well as Mexico and the Caribbean from the global research scheme and international collaborative projects. Fortunately, very recently, valuable initiatives have started to consolidate and give a much needed impulse to this area of research.

LAC has a peculiar amalgam of people with Indigenous and European origin, together with African ancestry in some of its countries, what makes this vast region a genetic melting pot with an enormous research potential. It is also a region of interest from an environmental standpoint, as it shares broad cultural commonalities, while keeping an extremely rich diversity of local milieus. As such, the emerging contribution of twin research in LAC countries would be an important addition to the international research resources.

However, the record of twin registries in LAC has been, so far, irregular. Early initiatives included Chilean[69] as well as Cuban registries,[70] the latter comprising a large sample of >55,000 twins, but, as yet these registries have not published any research results in peer-reviewed international scientific journals. More recently, a parallel initiative appeared in Brazil: the University of Sao-Paulo Twin Panel,[71] which was closely followed by two incipient registries in Mexico: the Mexican Twin Registry[72] and TwinsMX.[73] This has opened new perspectives for twin studies in LAC countries, and as they increase in size, they should be able to make meaningful contributions to twin studies in the near future.

3.3 International consortia

The fact that many twin registries collected similar phenotypic and genotypic information allows for meaningful collaborations between the registries, offering the opportunity to increase statistical power by increasing sample size and to study interactions between genes and exposures to diverse environmental conditions. One of the early collaborative efforts pooled Nordic population-based twin registries (Denmark, Finland, Norway, and Sweden) linked with the country-specific national cancer and cause-of-death registries to analyze the heritability of cancer incidence.[74] This consortium (NorTwinCan) has recently been re-established (NorTwinCan) to include more than 300,000 twins and 58 years of follow-up, on average, and studies the genetic and environmental etiology of cross-cancer associations.[75]

Interplay of Genes and Environment across Multiple Studies (IGEMS) is a consortium of 18 twin studies from 5 different countries (Sweden, Denmark, Finland, United States, and Australia) established to investigate the nature of gene-environment (GE) interplay in physical and psychological functioning, dementia, and mortality.[76] Fifteen of these studies are longitudinal, with follow-up as long as 59 years after baseline. The IGEMS now includes over 76,000 participants aged 14–103 years at intake.

A major effort in the field of comparative twin studies was Genome EU twin consortium combining twin data from seven European countries and Australia.[77] This project led to a series of papers comparing heritability estimates for a number of traits across the countries, showing that participating countries are very similar in heritability for height, BMI, and sport participation. This project was further continued within the European Network for Genetic and Genomic Epidemiology (ENGAGE Consortium) focusing more on molecular genetics.[78] The largest collaborative consortium to date is the COllaborative project of Development of Anthropometrical measures in Twins (CODATwins) which as its target to pool together all twin cohorts in the world having information on body composition, parental and own education, and smoking.[79] Currently, the CODATwins database includes around 1 million height and weight measures on almost 500,000 twins from 54 twin projects representing 24 countries. In addition, many of the twin registries also contribute to consortia, which are not twin-specific, by adding their data or the outcomes of genomewide association analyses to those of non-twin populations, thereby increasing the power for gene finding.

3.4 Concluding remarks

Twin registries have come a long way from the establishment of the first register in 1954. As illustrated in Fig. 3.1 and Table 3.1, twin registries are now present across the entire world, though with a focus on Western societies. While it will be important to ensure other parts of the world will be better represented, the wealth of data available in combination with the large sample size presents a source of important scientific findings.

The phenotypes studied in the registries cover almost all types of behavioral traits as well as mental health and various complex diseases. Notable is that several twin family registries are able to link their cohorts with national demographic, social, and public health registries, which may not only help in increasing their sample sizes and the representativeness of the population under study but may also further enrich the data available for individuals in the registry. Consistent with current trends in genetic research, a growing number of twin registries have been incorporating molecular genetic measures to the spectrum of available information. Many of them now include data from genome-wide or exome microarrays, whole-genome sequencing, or methylation analyses. Together with the impressive amount of phenotypical information accumulated, this has enhanced the already high potential for collaboration, both nationally and internationally, of twin registries.

The biggest threat for twin registries is a lack of funding. Setting up and maintaining a twin family register requires a long-term financial commitment which few institutions are prepared to make and many registries are therefore dependent on research grants to keep the twin registry going. The fact that so many twin registries are still ongoing and new registries still emerge is evidence of the great scientific value represented by twin registries.

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