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The Sri Lankan Twin Registry: 2012 Update

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The Sri Lankan Twin Registry (SLTR), established in 1997, is a unique resource for twin and genetic research in a low- and middle-income country (LMIC). It comprises of a volunteer cohort of 14,120 twins (7,060 pairs) and 119 sets of triplets, and a population-based cohort of 19,040 (9,520 pairs) twins and 89 sets of triplets. Several studies have been conducted using this registry, including the Colombo Twin and Singleton Study (CoTaSS 1; 4,387 twins, 2,311 singletons), which have explored the prevalence and heritability of a range of psychiatric disorders as well as gene-environmental interplay. Currently, a follow-up study (CoTaSS 2) of the same cohort is underway, looking at the prevalence and interrelationship of key cardiovascular and metabolic risk markers (e.g., metabolic syndrome). A significant feature of CoTaSS 2 is the establishment of a biobank. Current SLTR work is extending beyond mental health and the interface between mental and physical health to new horizons, extending collaborations with the wider global twin research community. Ethics and governance have been given special emphasis in the initiative. Capacity building and public engagement are two crucial components. Establishment of a state-of-the-art genetic laboratory was a major accomplishment. SLTR is a classic showcase of successful North–South partnership in building a progressive research infrastructure in a LMIC.

■ **Keywords:** twin research, Sri Lanka, developing world, North-South collaboration, gene-environment interaction

Twin studies allow us to determine the degree to which traits and disorders are heritable within specific populations. Most of these studies use volunteer registries of twins, and most are in North America, Europe, and Australia (Boomsma et al., 2002). However, it is not known how far these findings are generalizable and applicable to developing countries, and application of twin study methods for cross-cultural comparisons is limited. Population-based registries are rare, even in the West (Boomsma et al., 2002). The uniqueness of the Sri Lankan Twin Registry (SLTR) lies in the fact of it being the first in the developing world (Sumathipala et al., 2000a, 2002). It is still one of the few large-scale, functioning population-based registries in the developing world (Van Dongen et al., 2012).

Brief History of SLTR

The development of a twin registry in Sri Lanka was proposed and initiated by AS in 1997 (Sumathipala et al., 2002). The objective was to establish a nation-wide twin registry, starting initially as a volunteer registry, and subsequent development of a population-based registry. It was envisaged that it would become a platform for a multidisciplinary approach toward twin research in the low- and middle-income country (LMIC) context. The evolutionary process of the SLTR has been reported previously (Siribaddana et al., 2006; Sumathipala et al., 2000a, 2002).

Several strategies for twin recruitment were employed; initial enrolling of volunteer twins through media campaigns was followed by tracing of twins through birth

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TABLE 1

Age Group Description of Volunteer Twin Cohort

Volunteer twin cohort (excluding triplets)					
	Gender				
Age group	Male–male	Female–female	Male–female	Missing	Total pairs
Below 10	161	189	109	0	459
11–20	899	1,032	642	6	2,579
21–30	738	867	449	3	2,057
31–40	319	487	279	7	1,092
41–50	162	197	134	5	498
51–60	59	77	73	3	212
61–70	33	47	25	0	105
71–80	10	15	13	2	40
Above 81	4	4	4	1	13
Age not known	1	4	0	0	05
	2,386	2,919	1,728	27	7,060

TABLE 2

Age Group Description of Population-Based Twin Cohort

Population-based twin cohort (excluding triplets)					
	Gender				
Age group	Male–male	Female–female	Male–female	Missing	Total pairs
Below 10	290	249	204	34	777
11–20	689	749	466	60	1,969
21–30	612	637	441	83	1,773
31–40	571	647	508	110	1,836
41–50	451	468	415	146	1,480
51–60	263	297	276	118	954
61–70	118	152	128	77	475
71–80	36	65	45	46	192
81+	22	18	05	19	64
	3,052	3,282	2,488	698	9,520

registration records and conduction of population-based recruitment (Sumathipala et al., 2000a, 2001, 2003). Therefore, the SLTR has mainly a volunteer cohort and a population-based cohort (Siribaddana et al., 2006; Sumathipala et al., 2000a, 2002).

The SLTR is a sustainable program, established through a strategic, multidisciplinary partnership between the Institute for Research and Development (IRD) and Institute of Psychiatry, King's College London. This initiative was mainly built upon competitive and substantial funding from the Wellcome Trust.

Current Status of the SLTR

Volunteer Cohort

This was established by recruiting twins through a national newspaper advertising campaign, as an island-wide registry. The SLTR volunteer cohort has 14,120 twins (7,060 pairs) and 119 sets of triplets registered. The age range is from 1 to 85 years. However, 72% of twins are less than 30 years of age. It comprises of 2,386 male–male, 2,919 female–female, and 1,728 male–female twin pairs. Gender details are not available for 27 twin pairs. Triplets comprise of 23 all male sets, 36 all female sets, and 59 mixed gender sets. Details are missing for 1 set. Zygosity identification has not been carried out for the volunteer cohort. Further details of gender and age groups are given in Table 1.

Population-Based Cohort

This is confined only to the Colombo district. The SLTR population-based cohort has 19,040 twins (9,520 pairs) and 89 sets of triplets registered. The age ranges from 6 to 96. Twins comprise of 3,052 male–male, 3,282 female–female, and 2,488 male–female pairs. Gender details are missing in 698 pairs. Triplets comprise 25 sets of all males, 39 sets of all females, and the rest of mixed gender. Further details on gender and age groups are also given in the Table 2. Zygosity was ascertained only on twins who participated in the Colombo Twin and Singleton Study (CoTaSS 1). There were 2,274 dizygotic pairs and 1,691 monozygotic pairs; information was missing for 30 (total 3,995). Details are given in Table 3. The overlap between the island-wide volunteer cohort and population-based Colombo district cohort is 334 twins.

Zygosity Assessment

Translation, adaptation, and preliminary validation of a zygosity determination questionnaire by Ooki et al. (1993) were undertaken at the outset (Sumathipala et al., 2000b). However, this questionnaire was not validated against the

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TABLE 3
Zygosity and Age Group Breakdown of Twin Participants in CoTaSS 1

Age group	MZ	DZ	Missing	Total
11–20	4	8	0	12
21–30	599	678	7	1,284
31–40	494	629	6	1,129
41–50	307	444	7	758
51–60	186	318	3	507
61–70	67	143	6	216
71–80	28	42	1	71
81+	6	12	0	18
	1,691	2,274	30	3,995

gold standard using genetic markers. We are in the process of completing this work, utilizing DNA extracted from buccal cells.

Specific Research Based on the Population Cohort

The CoTaSS 1

The main objectives of this study were to: (1) identify a representative population-based twin sample in Colombo district of Sri Lanka; (2) describe the prevalence of psychiatric disorders within the twin sample and a parallel singleton sample which is a unique feature of this specific study; (3) estimate the heritability of common mental disorders within the twin study; (4) explore the interplay between genetic and environmental influences on psychiatric disorders. To date, seven papers have been published using data from CoTaSS 1 (Ball et al., 2009, 2010a, 2010b, 2010c, 2011; Siribaddana et al., 2008; Zavos et al., in press). The key findings to date are summarized below.

Prevalence of Psychiatric Disorders

One of the main aims of CoTaSS 1 was to establish the prevalence of psychiatric problems in a representative sample of twins and singletons from the Colombo district of Sri Lanka. Findings for depression indicate that the prevalence is lower than in many Western countries, although symptom patterns were similar. A significant interaction was observed between gender and risk factors such as low education and low access to material resources (Ball et al., 2010a; Siribaddana et al., 2008). These risk factors were strongly associated with depression in men.

A quarter of the sample had abnormal fatigue (Ball et al., 2010c). The associated risk exposures were similar to those of depression and included early school leaving, poor standard of living, life events over the past 12 months, and parental neglect. Prevalence of substance use problems, including tobacco use, varied substantially by gender (Zavos et al., 2012).

Heritability of Common Mental Disorders

Overall, a very similar pattern of heritability has been shown in the current sample compared with results from twin studies in western countries for depression, fatigue, and tobacco use (Ball et al., 2009, 2010c; Zavos et al., 2012). However, some differences were noted. For example, the heritability of a broad depression diagnosis was found to be significantly lower in men compared to women in this population, and this heritability was lower than most studies in Europe, Australia, and North America (Ball et al., 2009).

Gene-Environment Interplay

We investigated a range of environmental exposures and their genetic or environmental contribution to depression and fatigue (Ball et al., 2010a). Gene-environment correlation was evident for some of the measured environments. Early school leaving and standard of living showed environmentally mediated effects on depression in men. In women, life events were associated with depression partly through genetic pathways. For fatigue, there were environmentally mediated effects and strong suggestions of family-environmental influences.

Involving a parallel singleton sample allowed us to report current and lifetime prevalence rates of psychiatric disorders in Sri Lanka. Comparison with the twin sample suggested that prevalence rates in twins were representative of the wider population, once adjusted for factors such as age (Ball et al., 2010a, 2010b; Zavos et al., 2012).

CoTaSS Follow-Up Study (CoTaSS 2)

Previous research has provided evidence of an association between cardiovascular disease, diabetes, and depression (Katon et al., 2005). In the CoTaSS 2, we are exploring the prevalence and interrelationship of a number of key cardiovascular and metabolic risk markers (e.g., metabolic syndrome). Diabetes, heart disease, and depression have become significant public health priorities in Sri Lanka. Therefore, an investigation into the extent of overlapping genetic and environmental influences is a timely requirement.

The main aims of the CoTaSS 2 are: (1) estimating the prevalence of the component phenotypes which make up 'metabolic syndrome' in Sri Lanka; (2) investigating the genetic architecture of metabolic syndrome phenotypes, and estimate the extent to which phenotypic correlations are explained by shared genetic or environmental effects; (3) determining whether there is a significant etiological overlap between depression and the component phenotypes of metabolic syndrome.

The CoTaSS 2 study was initiated in May 2012, 5 years after the completion of the CoTaSS 1 study data collection. We have successfully managed to trace around 1,600 twins of baseline sample, and have completed 1,336 questionnaire interviews by mid-October 2012. The response rate is around 83%. Collection of biological material (blood) was started at a later stage and is currently in progress. Table 4 presents a summary comparison of CoTaSS 1 and 2 study attributes.

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TABLE 4
Comparative Attributes of CoTASS 1 and CoTaSS 2

	CoTaSS 1	CoTaSS 2
Study design	Population based Twin and singleton study	Population based Twin and singleton study
Age range of twins	15–85 years	16 years and above
Sample size (selected)	4,387 twins and 2,311 non-twins singletons	Currently traced 1336 twins
Sample size (participated)	4,024 (91.7%) twins and 2,019 (87.4%) singletons	Currently recruiting
Instruments	Zygosity questionnaire, Section A of Composite International Diagnostic Interview (CIDI), Bradford Somatic Inventory, Short Form (SF)-36, Chalder Fatigue scale, Life events, Childhood Experience of Care and Abuse Questionnaire (CECA-Q), Suicidal ideations, War and Tsunami questionnaire, CIDI B, D, E, J, K Sections	CIDI depression (12 months), smoking information, international physical activity questionnaire, closeness among twins questionnaire, Food frequency, Generalized Anxiety Disorder assessment (GAD-7), PTSD Checklist (PCL-17), SF-36, Beck Depression Inventory (BDI), Stressful Life Events, Multi Dimensional Support Scale (MDSS), Chalders Fatigue Scale, Bradford Somatic Inventory (BSI), Pittsburgh sleep quality index, Alcohol Use Disorders Identification Test (AUDIT)
Biochemical tests/markers	Not collected	Fasting blood glucose and insulin, Adiponectin, glycosylated haemoglobin, lipid profile, SGOT (liver enzymes), creatinine (renal function), highly sensitive–C reactive protein, IL- 665, plasma ascorbic acid, Urine albumin/creatinine ratio
Phenotypes	CMD, affective disorders, anxiety, fatigue, PTSD, and substance misuse/dependence	Depression and Metabolic syndrome, anthropometric measures, fasting insulin, adiponectin, glycosylated hemoglobin, diet, and physical activity
Zygosity assessment	By questionnaire (DZ 2,274, MZ 1,691)	By questionnaire
Risk factors of interest	Early experiences of abuse and neglect, war and tsunami exposure, environmental exposures including socio-economic status, poverty related/ deprivation variables, poor educational attainment, life events	Raised triglycerides, reduced HDL cholesterol, hypertension, and raised fasting blood glucose
Outcomes	Life-time prevalence rates of psychiatric disorders, heritability of common mental disorders, gene-environment interplay	Metabolic syndrome and its relationship with psychiatric disorders

A sub-study within the CoTaSS 2 phase aims to evaluate the contribution of sleep and activity levels to the prevalence of metabolic syndrome and depression in Sri Lanka, using self-report and actigraphy. It is led by NG and will be the first study to determine population-based estimates of validated sleep parameters in a developing country (Stranges et al., 2012).

Major Goals of the SLTR

We look to extend our current work beyond mental health, and interface between mental and physical health. Through the CoTaSS 2, we have obtained the necessary ethical clearance for biobanking DNA and serum/plasma. We intend to engage in epigenetic, genome-wide association, and candidate gene studies. Through these studies, we are looking to expand our horizons and extend our collaboration with the wider global twin research community. We look forward to working with the international twin research community in twin data harmonization. Gradual expansion of the existing Colombo-based registry to rest of the country is also being targeted.

Since inception, our strategic agenda has been to work toward a sustainable center of excellence in twin and genetic research in a LMIC through North–South collaboration. We thereby aim to expand the twin research program through multidisciplinary and cross-disciplinary approaches. Capacity building in relevant expertise is an integral part in our initiative.

In keeping with one of our primary targets set at the inception of SLTR, we have established a state-of-the-art genetic laboratory.

Ethics and Governance

The SLTR has huge potential as a unique resource due to its location, size, and design. However, as it is from a resource-poor country it could be vulnerable to exploitation for easy and cheap research. In order to protect the SLTR and its registrants, we followed carefully designed ethical and governance frameworks, which have been developed in parallel to SLTR (Sumathipala et al., 2002).

Initially, ethical clearance was obtained from ethics committees at the Faculty of Medicine, University of Colombo and the Institute of Psychiatry, London (Sumathipala et al., 2000a). For the CoTASS 1 study, ethical clearance was obtained from the Institute of Psychiatry, London, Sri Jayewardenepura University Ethics Committee, Sri Lanka, and also from the WHO's Ethics Committee (Siribaddana et al., 2006). For the CoTaSS follow-up study and the biobank, ethical clearance was obtained from the Institute of Psychiatry, London, and the Sri Jayewardenepura University Ethics committee.

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Specific National and Regional Issues

Cultural attitudes toward twins have not been specifically studied in Sri Lanka. Even though not systematically investigated or documented, there is indirect evidence of a negative attitude toward genetic research in Sri Lanka. There have been a few media reports on exporting genetic material, portrayed as an exploitation of Sri Lankan genetic heritage. Therefore, since the beginning of the SLTR, being sensitive to cultural and social challenges has been our credo. To this end, establishing the genetic lab was a major strategic accomplishment.

Public Engagement

Public engagements have been one of the core themes running through all of the work conducted at the IRD, which houses the twin registry as one of its main research programs. SLTR public engagement work includes publishing regular newsletters for twins, using the IRD trilingual journal to create awareness about twin research among the public, and a Wellcome Trust-funded 3-year project (Multiples Engage in Research through Culture — MERC) led by SS and AS.

Discussion

Scarcity of research capacity in LMIC has been well established (Patel, 2007; Razzouk et al., 2010; Siriwardhana et al., 2011). However, the SLTR and the wider IRD initiative have showcased how successful North–South partnerships can overcome barriers to minimize the 10/90 divide (where 90% of global research funding targets the disease burden of only 10% of world population; Siriwardhana et al., 2011). This is especially poignant considering the facts that twin research concept was novel to Sri Lankans, the existing scarcity of research funding and lack of local expertise in twin method. However, in a perfect example of North–South collaboration, support and expertise came from colleagues at King's College London to establish SLTR and ensure its sustenance.

Author Contributions

Authorships are given in descending order of seniority with the SLTR starting with AS.

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