COHORT PROFILE

Cohort Profile: Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study

Shu-E Soh,1,2 Mya Thway Tint,3 Peter D Gluckman,4,5 Keith M Godfrey,6,7 Anne Rifkin-Graboi,4 Yiong Huak Chan,8 Walter Stüenkel,4 Joanna D Holbrook,4 Kenneth Kwek,9 Yap-Seng Chong,3 Seang Mei Saw1* and the GUSTO Study Group

1Saw Swee Hock School of Public Health, National University of Singapore, Singapore, 2Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, 3Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore, 4Singapore Institute for Clinical Sciences, Agency for Science and Technology Research (A*STAR), Brenner Centre for Molecular Medicine, Singapore, 5Liggins Institute, University of Auckland, Auckland, New Zealand, 6Medical Research Council Lifecourse Epidemiology Unit, Southampton, UK, 7NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK, 8Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, Singapore and 9KK Women’s and Children’s Hospital, Singapore

*Corresponding author. Saw Swee Hock School of Public Health and Yong Loo Lin School of Medicine, National University of Singapore, E-mail: seang_mei_saw@nuhs.edu.sg

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Why was the cohort set up?

Modern lifestyles and nutritional transition have given rise to an emerging epidemic of obesity and type 2 diabetes in developed and developing countries.1,2 In general, metabolic compromise is seen in South Asians at relatively lower levels of obesity compared with Europeans, with Chinese having an intermediate relationship, suggesting that the patterns of development of obesity and metabolic function in different Asian populations merits focused investigation.3

The prevalence of type 2 diabetes in Singapore has increased from 1.9% in 1975 to 11.2% in 2010, and is now one of the highest in the developed world.4 The three major Singaporean ethnic groups, Chinese, Malays and Indians, appear to have distinct susceptibilities leading to differing metabolic risk.5 Such differences may be genetic, developmental or cultural in origin. The pathways leading to insulin resistance, obesity and related traits are complex and derive from an interplay of genomic and environmental factors operating over the lifespan, including during early development.6 Environmental cues such as maternal nutrition can have important effects on foetal gene expression and have shown to influence developmental plasticity7 via epigenetic processes.8 In recent years, major epigenetic pathways involving histone and DNA modifications have been unravelled and more technological tools developed to study their function.9,10 It has recently been reported that it may be of value to measure epigenetic changes in DNA derived from foetal tissues at birth, such as umbilical cord.11 Hence, we wished to examine whether specific epigenetic marks have utility as biomarkers for identifying babies that are ‘programmed’ in utero to develop obesity or non-communicable diseases later in life.11,12 A set of epigenetic biomarkers would allow clinical intervention at early stages in individuals at risk, thereby enabling prevention of obesity and metabolic diseases.13

The Growing Up in Singapore Towards healthy Outcomes (GUSTO) study comprises one of the most carefully phenotyped parent-offspring cohorts with a particular focus on epigenetic observations and detailed study in the first years of life, enabling examination of the potential roles of foetal, developmental and epigenetic factors in pathways to disease.

The primary objective of the GUSTO cohort study is to evaluate the role of influences operating during early development, affecting pathways to metabolic compromise and altered body composition. Secondary objectives are:

(i) To identify maternal determinants of the offspring’s epigenetic state and associations with
other indices of early life experience that may influence growth and body composition.

(ii) To evaluate risk factors and potential epigenetic biomarkers for allergic disorders.

(iii) To evaluate the predictors of retinal vasculature development in utero and during postnatal life, and to determine relationships between early life factors and early refractive error development, including the potential role of epigenetic processes.

(iv) To understand pre- and postnatal influences on individual differences in neurocognitive and emotional development and their relation to somatic growth and metabolic health.

Who is in the cohort?

The GUSTO study recruited pregnant women aged 18 years and above, attending their first trimester antenatal dating ultrasound scan clinic at Singapore’s two major public maternity units, namely National University Hospital (NUH) and KK Women’s and Children’s Hospital (KKH) between June 2009 and September 2010. The participants approached were Singapore citizens or permanent residents who were of Chinese, Malay or Indian ethnicity with homogeneous parental ethnic background and who had the intention of eventually delivering in NUH or KKH and residing in Singapore for the next 5 years. Mothers receiving chemotherapy, psychotropic drugs or who had type I diabetes mellitus were excluded. Only women who agreed to donate birth tissues including cord, placenta and cord blood at delivery were included. Informed written consent was obtained from each participant.

We screened 3751 families, of which 2034 met eligibility criteria. The reasons for the ineligibility of 1717 families are listed in Supplementary Table 1 (available as Supplementary data at IJE online). Ineligibility was principally due to an intention to deliver outside the two study hospitals or not to remain in Singapore for the next 5 years, looking beyond the first trimester, or non-homogeneous parental ethnic background. Of the 1247 women (response rate 61.3%) recruited, 1162 conceived naturally and 85 conceived through in vitro fertilisation (IVF). At baseline, 55.9% were Chinese, 26.1% Malay and 18.0% Indian. Mean maternal age at recruitment was 30.6 years (range: 18–46 years). The ethnic background of those not recruited differed somewhat [61.3% Chinese, 14.2% Malay and 24.5% Indian (P = 0.042 compared with responders)], with a similar mean age of 31.5 years [range: 18–48 years (P = 0.085)].

A total of 1176 babies were born. The first baby was born on 30 November 2009 and the last baby was born on 1 May 2011. Figure 1 shows the flow chart of the progress of participants through the study.

How often have they been followed up?

The women returned to the hospital at 19–21, 26–28 and 32–34 weeks of gestation for ultrasound scans to assess gestational age and foetal growth. Detailed interviews were conducted in the clinic at recruitment and at 26–28 weeks gestation. Birth tissues were obtained at delivery and anthropometric measurements of the newborn made within 24 h of birth. During infancy, the babies are examined at home at 3 weeks, 3 months and 3-monthly thereafter until 15 months of age. The children are then seen at the study clinic at 18, 24 and 36 months. Further follow-up is planned for later childhood. The current attrition rate is 12.7%, with most participants having withdrawn before or soon after delivery. During pregnancy, 70 participants (5.6%) dropped out primarily for the following reasons: (i) lost to follow-up (n = 15, 1.2%); (ii) family disapproval (n = 10, 0.8%); (iii) personal reasons (n = 36, 2.9%); and (iv) inconvenience (n = 7, 0.6%). After delivery, 88 participants (n = 7.1%) withdrew voluntarily because of personal or family circumstances. Families continuing in the study have a similar ethnicity profile to those recruited but, in keeping with most birth cohort studies, tend to have slightly higher household monthly income, maternal age and educational attainment (Supplementary Table 2, available as Supplementary data at IJE online).

What has been measured?

Table 1 specifies the information collected at each study visit.

Antenatal period

(i) General questionnaire and physical examination

At the recruitment visit (<14 weeks) and at 26–28 weeks of gestation, questionnaires were administered to the women to capture demographic, socio-economic, lifestyle, maternal well-being, obstetric and medical history data. Anthropometric measurements included skin fold thicknesses and mid upper arm circumference, performed at 26–28 weeks of gestation.

Pulse wave analysis was measured to derive the maternal central aortic systolic pressure, radial augmentation index and a range of other indices from the radial pulse. Autorefraction and fundus photography were conducted to assess changes in the mothers’ retinal vessel diameters during pregnancy. Routine antenatal clinical and laboratory data were abstracted from the hospital case notes, including measurements of weight, blood pressure, full blood count and urine dipstick.

Maternal well-being was assessed using the Edinburgh Postnatal Depression Scale which has been validated in Singapore women. The
State-Trait Anxiety Inventory and Beck Depression Inventory were also administered in conjunction with the Pittsburgh Sleep Quality Index. A series of questionnaires was used to assess maternal childbearing attitudes and social support. Maternal well-being and postnatal affective state were assessed 3 months after delivery and reassessed at the 12-, 24- and 36-month visits.

Interviewer-administered questionnaires and prospective 3-day diaries were administered at 26–28 weeks of gestation to assess maternal dietary intakes and patterns. Patterns of maternal diet during the confinement period have unique Asian characteristics and were determined at 3 weeks postpartum. The confinement period is practised by major Asian ethnic groups for about 30 days immediately following delivery, when women are confined to their homes and observe a broad set of restrictions on their diet and activities.15

Blood was collected for an oral glucose tolerance test at 26–28 weeks of gestation and analyses of other biochemical markers. Hair samples were collected for toxicology screening (exposure to lead, metals) and to determine steroid levels. Buccal swabs were collected for DNA to investigate the role of epigenetic processes.

(ii) Foetal biometry

Intrauterine growth parameters, namely foetal biparietal diameter, head and abdominal...
Table 1 Data collected at each stage of the GUSTO birth cohort study

<table>
<thead>
<tr>
<th>Antenatal (weeks)</th>
<th>Postnatal</th>
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<tbody>
<tr>
<td>Recruitment</td>
<td>Week</td>
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<td>&lt;14</td>
<td>3</td>
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<tr>
<td>19-21</td>
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<td>26-28</td>
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<td>32-34</td>
<td>12</td>
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<tr>
<td>Delivery</td>
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<td>3</td>
<td>18</td>
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<td>6</td>
<td>24</td>
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**Mother**
- Demographics/social
  - Ethnic group
  - Marital status
  - Housing, income, education
  - Occupation/employment
- Lifestyle
  - Activity and exercise
  - Alcohol and smoking
- Diet
  - Prospective 3-day diet record
  - Food supplements
  - General diet questions
- Health
  - General health
  - Allergy history
  - Menstrual cycle
  - Medications
  - Appetite and nausea
  - Maternal depression
  - Family medical history
- Body composition
- Biological samples
  - Buccal swab & hair
  - Blood
  - Breast milk
- Obstetrics
  - Delivery/labour
  - Obstetric history
  - BP/weights/urine analyses
  - Oral glucose tolerance test
  - Pregnancy complications
- Pulse wave velocity (BP)
- Retinal photograph
- Autorefraction

**Father**
- Demographics/social
- Health & allergy history
- Height/weight/date of birth
- Biological sample: buccal swab
- Autorefraction

(continued)
circumferences and femur and humerus lengths, were assessed by ultrasonography at 11–12, 19–21, 26–28 and 32–34 weeks of gestation. Scans were conducted in a standard manner at both hospitals by trained ultrasonographers.

**Table 1**

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<td>36</td>
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<table>
<thead>
<tr>
<th>Infant/Child</th>
<th>Postnatal</th>
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<tr>
<td>Foetal anthropometry</td>
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<tr>
<td>Infant data &amp; neonatal problems</td>
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<tr>
<td>Body composition</td>
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<td>Body measurements</td>
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<td>Bioelectrical impedance analysis</td>
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<td>PEA POD</td>
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<tr>
<td>Magnetic resonance imaging</td>
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<td>Diet</td>
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<td>Milk or formula feeding</td>
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<td>Food freq/preference</td>
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<td>Prospective 3-day food diary</td>
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<td>Introduction of foods</td>
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<td>Eating behaviour/dietary restraint</td>
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<td>Medications &amp; supplement use</td>
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<td>Illnesses &amp; allergies</td>
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<td>Skin prick testing</td>
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<td>Dental eruption &amp; Oral health</td>
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<td>Immunization record</td>
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<tr>
<td>Environment</td>
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<tr>
<td>Cognitive function</td>
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<td>Developmental milestones/language</td>
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<td>Sleep/activity</td>
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<tr>
<td>Biological samples</td>
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<td>Umbilical cord, placenta, blood</td>
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<tr>
<td>Buccal swab</td>
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<td>Nasal swab</td>
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<td>Faecal sample</td>
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's' indicates that a subset of the participants underwent the measures at this timepoint.

After delivery, body composition of the neonate was assessed by anthropometry. Subsequently the percentages of neonatal fat and fat-free mass were assessed using bioelectrical impedance analysis (BIA) and PEA POD non-invasive air-displacement plethysmography. Many of the babies \( (n=388) \) underwent whole body magnetic resonance imaging (MRI), including brain and eye imaging, at age 7–10 days and a small number at 6 weeks \( (n=30) \) and 6 months \( (n=50) \) to document adipose tissue distribution and organ size. Abdominal adipose tissue is segmented and quantified as superficial subcutaneous, deep subcutaneous and internal depots.

**After delivery till 3 years of age**

**i) Metabolic, neurodevelopmental and related outcomes**

After delivery, all routinely recorded birth data including birthweight, gestational age and neonatal problems were abstracted from the case notes. A key feature of the GUSTO study is the collection of body fat measures on all infants. Within the first 24 h after delivery, body composition of the neonate was assessed by anthropometry. Subsequently the percentages of neonatal fat and fat-free mass were assessed using bioelectrical impedance analysis (BIA) and PEA POD non-invasive air-displacement plethysmography. Many of the babies \( (n=388) \) underwent whole body magnetic resonance imaging (MRI), including brain and eye imaging, at age 7–10 days and a small number at 6 weeks \( (n=30) \) and 6 months \( (n=50) \) to document adipose tissue distribution and organ size. Abdominal adipose tissue is segmented and quantified as superficial subcutaneous, deep subcutaneous and internal depots.

Infant formula feeding and breastfeeding patterns, including brands of formula milks, volume, duration,
partial vs exclusive breastfeeding and expressed vs direct breast milk, have been ascertained to analyse relations with outcome measures. The infant’s weaning diet has been assessed using 3-day food diaries and interview-administered questionnaires at ages 6, 9 and 12 months, with portion size picture guides customized for this age group. The toddler’s diet is assessed further at 15, 18, 24 and 36 months of age using food diaries and interview-administered food frequency and preferences questionnaires.

Serial anthropometric measures of early growth trajectories and BIA are made in the child’s home by trained observers. Health status (including oral health) of the child is recorded via interviews at each visit. In addition, any interim illnesses including infections and respiratory diseases are recorded and the relevant case notes traced from the hospital if necessary. Atopic dermatitis, allergic rhinitis, asthma and food allergy symptoms are monitored for the development of allergic outcomes.16 Skin prick testing using relevant allergens is carried out as clinically indicated and at ages 18 and 36 months. Cycloplegic autorefraction is performed on the child at age 36 months to measure refractive error.

Facial imitation tests and electroencephalography were conducted within 24 h after delivery to assess their potential value as measures of cognitive development in the neonatal period. A subset of the participants (n = 532) have undergone extensive neurocognitive phenotyping including electroencephalography and eye tracking, at 6, 18 and 36 months of age, and were administered the Bayley Scales of Infant and Toddler Development at the 24-months visit. The majority are regularly assessed for developmental milestones in areas of cognition, behaviour, language and gross and fine motor skills at each visit until 36 months of age.

(ii) Biospecimens

Rinsed umbilical cord, cord blood and placenta were obtained at delivery by trained personnel to enable investigation of epigenetic processes. Breast-milk samples were collected at 3 weeks, 3 and 6 months after delivery in breastfeeding mothers. For the children, stools specimens are collected from birth up to 24 months of age to assess evolution of gut microbiota. Buccal swabs are collected at each visit for DNA analysis. Nasal swabs for cytology smears and molecular studies for respiratory viruses are taken where indicated and at the regular visits. Buccal swabs are collected from the fathers at the 24-months visit.

Molecular and epigenetic analysis

The primary hypothesis to be evaluated is that the in utero and early life environments influence the epigenome, which in turn influences patterns of growth, body composition and development in infancy and childhood. Biological specimens such as umbilical cord and buccal swabs from infants taken longitudinally are analysed by genome-wide methodologies for RNA expression and DNA methylation characterization. Methods to survey the latter include the Illumina Infinium Methylation human 450 K bead array,17,18 a bead-based technology for genome-wide methylation analysis, as well as reduced representation bisulfite sequencing (RRBS) and other next-generation sequencing methodologies.19,20 Candidate marks are technically repeated and statistically validated in larger specimen numbers by pyrosequencing (Qiagen) and Sequenom (Sequenom)-based technologies for DNA methylation, and quantitative real-time reverse transcription polymerase chain reaction (RT-PCR) for gene expression studies. Gene expression and DNA methylation data are analysed, processed and integrated with genotype and clinical data at the pathway, gene and base level. Associations of epigenetic marks with clinical data are discovered via multivariate analysis controlling for false discovery rate. Pathway and network analysis is used to enrich for true positives and to build mechanistic hypotheses that can be tested in model systems.

What has it found? Key findings and publications

At recruitment, 58.5% of the mothers had completed GCE A levels or polytechnic education and 46.3% were expecting their first child. The mean self-reported pre-pregnancy BMI of GUSTO mothers was 22.7 kg/m² (SD = 4.5); however, 25.3% were overweight and 12.5% were obese prior to pregnancy. In all, 7.9% of the women scored above 15 on the Edinburgh Depression Scale (EPDS) administered at 26 weeks’ gestational age, suggesting they could be suffering from a depressive illness; 2.3% of women smoked; and 1.6% of women consumed alcohol during pregnancy. Elevated blood pressure, greater pre-pregnancy and pregnancy BMI were found to be associated with a range of adverse retinal arteriolar changes in pregnant women, suggesting an effect of maternal obesity and blood pressure on the microcirculation.21,22

As the cohort’s youngest offspring was born in May 2011, analyses are now possible. Early conclusions from the neonatal imaging and molecular studies have been reached. Among Chinese, Malay and Indian neonates, brain morphological shape and white matter microstructure differences, especially anatomical variations in the spinal-cerebellar and cortical-striatal-thalamic neural circuits associated with sensorimotor functions, were observed using MRI and diffusion tensor imaging.23 Sexual dimorphism of the basal ganglia and thalamus during neonatal period has been found which differs from that found in older children and adults, suggesting that regionally distinct patterns of postnatal brain development between males and females are due to ongoing neurodevelopmental processes after birth.24
DNA from GUSTO umbilical cords shows good agreement between Illumina Infinium Methylation human 450 K bead array and RRBS. We have found that the umbilical cord transcriptome is substantially influenced by gestational age even within the normal range. The effect of gestational age is far stronger than that of birthweight even when extreme birthweights are studied (Figure 2). The RNA expression changes dependent on gestational age are enriched in signal transduction pathways, such as Hedgehog and cytokine signalling.

What are the main strengths and weaknesses?

There is a paucity of high-quality data on foetal and early life outcomes in Asian populations. The GUSTO study helps fill this gap with recruitment in the first trimester and tracking of development, growth and other parameters throughout the antenatal period, birth and the first 3 years of life, providing new insights into development in the early part of the human life course. Monitoring of infant growth is undertaken at more frequent time-points than in many other studies. This is further complemented by the assessment of body composition using multiple measurement methods including anthropometry, MRI, BIA and the PEA POD.

At birth, body composition has been assessed and epigenetic biomarkers in perinatal tissues is being analysed in an Asian population, providing an important opportunity to investigate the developmental pathways underlying variable disease risk in the three major ethnic groups. Serial postnatal buccal swabs are also collected to capture epigenetic changes in relation to environmental exposures.

During recruitment, the eligibility criteria were designed to allow examination of differences between ethnically homogeneous groups, to enable detailed characterization from early pregnancy onwards in two maternity hospitals and to maximize long term follow-up; as Singapore is a cosmopolitan city with inter-racial marriages and global mobility, only 54.2% met these criteria. The response rate of 61.3% (1247 families recruited) can potentially give rise to sampling bias and we evaluated the ethnic background and age of those recruited and not recruited. The ethnic background differed between these two groups as we had planned to complete the recruitment with a higher percentage of Malays than Indians. The mean ages were comparable. Retention in intensive longitudinal studies such as GUSTO is always challenging and we recognize that in all epidemiological studies, non-participants may differ from participants, but the exposure-disease relationships often hold. We believe that our home visit approach and other measures will minimize attrition through multiple methods, including frequent communications with the families.

The three distinct ethnic groups, Chinese, Malays and Indians, present in the Singaporean population, will allow us to examine associations between genomic variation and developmental-environmental interactions. This is important given the high concern about the predicted increase in metabolic diseases in emerging as well as developed Asian countries. Our programme is designed to integrate disciplines and institutions in Singapore in partnership with international collaborators, to address this important perspective.

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

Investigators interested in exploring the possibility of collaborations should contact lead principal investigator Associate Professor Chong Yap Seng (yap_seng_chong@nuhs.edu.sg), principal investigators Professor Saw Seang Mei (seang_mei_saw@nuhs.edu.sg), Professor Kenneth Kwek (Kenneth.Kwek.YC@kkh.com.sg) and Sir Peter Gluckman (pd.gluckman@auckland.ac.nz). GUSTO has a website, mainly focused on information for the participants, at http://www.gusto.sg/. More information is also available on the website of the Translational Clinical Research (TCR) Flagship Programme on Developmental Pathways to Metabolic Disease, which is commonly known as Developmental Origins: Singapore (DevOS), website http://devos.sg/.
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