Institution: London Metropolitan University		
Unit of Assessment: 10 Mathematical Sciences		
Title of case study: Centile and growth curves for global health monitoring and diagnostics		
Period when the underpinning research was undertaken: 2001 - 2007		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Robert Rigby	Researcher Associate Lecturer Professor of Mathematics	01.09.1979 - 30.09.2016 09.02.2017 - 19.01.2020 20.01.2020 - present
Mikis D. Stasinopoulos	Principal Research Fellow Reader Professor in Statistics Associate Lecturer Professor of Mathematics	01.09.1989 - 31.08.2007 01.09.2007 - 31.07.2011 01.08.2011 - 30.09.2016 08.02.2017 - 19.01-2020 20.01.2020 - present
Period when the claimed impact occurred: 1 August 2013 – 31 December 2020		
Is this case study continued from a case study submitted in 2014? Y		

1. Summary of the impact (indicative maximum 100 words)

The application of our novel GAMLSS statistical model and methodology has improved a wide range of areas of human health, especially – but not limited to – infants and children, through the adoption of our GAMLSS model to centile estimation and its advance on the previously standard LMS method. Centile curve charts are used by health and medical practitioners to monitor child growth and changes in the development of disease.

The GAMLSS methodology and software for centile and growth curve charts can provide a better fitting model distribution than previous models and allows for multiple explanatory variables, leading to more accurate centiles, and hence more accurate identification of patients with abnormal response variable values.

Centiles obtained from GAMLSS are used worldwide in a variety of medical applications, providing diagnostic tools for health monitoring to identify medical problems in individuals and populations and improving health globally, including the World Health Organisation's Child Growth Standards which are used in over 150 countries to formulate health and related policies including the identification of child malnutrition; and the Global Lung Function Initiative's more individual-specific centiles for lung capacity used in the diagnosis and treatment of respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD).

2. Underpinning research (indicative maximum 500 words)

Centile curve charts provide in one chart a set of curves for different percentiles of a dependent variable (e.g. height) against an explanatory variable (e.g. age). For example, for a 1 percentile (i.e.1%) curve of height against age, we would expect only 1% of healthy children to have a lower height than the curve, and 99% of healthy children to have a higher height, given their age. This is used to identify potential stunting.

More generally centile surfaces provide different percentiles for a dependent variable (e.g. lung capacity) against two (or more) explanatory variables (e.g. age and height).

For many years the most popular method for growth chart estimation was the LMS method, developed by Cole and Green (1992), which obtained centiles curves for a response variable, by

smoothly modelling the location, scale and skewness parameters of a *single* three parameter distribution, the Box-Cox Cole and Green distribution for the response variable, against a *single* continuous explanatory variable.

The restriction of LMS to a *single* distribution (which cannot model kurtosis, I.e. light or heavy tails of the distribution) often leads to inaccurate modelling of the response variable distribution, resulting in inaccurate and misleading centiles and the resulting misdiagnosis of abnormal values of the response variable. The restriction of LMS to a *single* explanatory variable often restricts the application of LMS or results in insufficiently accurate centiles. For example, lung capacity depends on age, height, sex and ethnic origin, and therefore centiles for lung capacity cannot be obtained by the LMS method.

In 2005, Rigby and Stasinopoulos developed the GAMLSS model which includes major generalizations of the LMS method of centile estimation. Rigby and Stasinopoulos generalized the LMS method to *any* response variable distribution and to modelling all the distribution parameters using *multiple* explanatory factors and/or linear or smooth functions of *multiple* explanatory variables, [R1]. The outcome of their research, the GAMLSS methodology and software, enables a better fitting model distribution and more explanatory variables for the response variable leading to more accurate centiles. Rigby and Stasinopoulos also provided a fitting algorithm for GAMLSS which they justified by proving that it maximised a penalised log likelihood function. [R1]

Rigby and Stasinopoulos developed the four parameter Box-Cox power exponential (BCPE) [R2], and Box-Cox *t* (BCT) [R3], distributions to provide more flexible distributions for the response variable, by allowing modelling of a kurtosis parameter in addition to the location, scale and skewness parameters. The kurtosis parameter can allow the modelling of heavy or light tails of the distribution. All four parameters of the distributions, for location, scale, skewness and kurtosis respectively, can be modelled using multiple explanatory variables. Rigby and Stasinopoulos [R2], [R3], also provided theoretical properties of the BCPE and BCT distributions.

The GAMLSS software, [R4], developed by Stasinopoulos and Rigby and written in the R language, is used worldwide to create and employ diagnostically centile and growth curve charts and surfaces, The GAMLSS software includes many functions specifically designed for creating, displaying and employing diagnostically centile charts, including functions for fan charts, centile comparison charts, calculating z-scores for an individual which can be monitored over time, and calculating and displaying residual multiple worm plots and Q statistics for assessing the adequacy of the fit to the data.

Rigby and Stasinopoulos's GAMLSS methodology and software provide academic researchers around the globe with a more general method for centile chart estimation, see section 4 for specific examples.

3. References to the research (indicative maximum of six references)

[R1] Rigby, R. A. and Stasinopoulos, D. M. (2005) Generalized additive models for location, scale and shape. (with discussion). Read paper to the Royal Statistical Society. *Applied Statistics*, **54**, 507-554. (https://doi.org/10.1111/j.1467-9876.2005.00510.x)

[R2] Rigby, R. A. and Stasinopoulos, D. M. (2004) Smooth centile curves for skew and kurtotic data modelled using the Box-Cox power exponential distribution. *Statistics in Medicine*, **23**, 3053-3076. (https://doi.org/10.1002/sim.1861)

[R3] Rigby, R. A. and Stasinopoulos, D. M. (2006) Using the Box-Cox *t* distribution in GAMLSS to model skewness and kurtosis. *Statistical Modelling*, **6**, 209-229. (https://doi.org/10.1191/1471082X06st122oa)

[R4] Stasinopoulos, D. M. and Rigby, R. A. (2007) Generalized additive models for location scale and shape (GAMLSS) in R. *Journal of Statistical Software*, **23**, 1-46. (https://doi.org/10.18637/jss.v023.i07)

The GAMLSS methodology for centile and growth curve estimation, developed by Rigby and Stasinopoulos and the GAMLSS software in R, developed by Stasinopoulos and Rigby, provide better centile estimates, leading to more accurate diagnosis of medical conditions, and hence better targeted treatment. The GAMLSS methodology has become the gold standard for producing centile and growth curve charts which are used worldwide, by international agencies such as the World Health Organization, and endorsed by national health organizations, including in the US, UK, Australia, Canada and Germany.

Since 2014, the real-world applications of GAMLSS have led to improvements in medical assessments resulting in benefits derived from the international standardization of child growth measurements, and in enhanced treatment and support planning for patients with chronic respiratory diseases:

World Health Organization (WHO) Child Growth Standards Growth assessment is used to monitor the health and nutritional status of children. In 2006, the World Health Organization selected Rigby & Stasinopoulos's GAMLSS methodology and software from over 30 competing methodologies to develop the WHO Child Growth Standards, because "GAMLSS allows for modelling the mean (or median) of the growth variable under consideration as well as other parameters of its distribution that determine scale and shape", [S3, p8]. They also stated: *"the BCPE method, with curve smoothing by cubic splines, was selected as the approach for constructing the growth curves. This methodology is included in a broader methodology, the GAMLSS*", [S3, p8]. The importance of this is that they use the Box-Cox power exponential distribution (BCPE), as well as GAMLSS and GAMLSS software in R.

Dr Elaine Borghi, statistician with WHO, confirmed that the WHO Child Growth Standards, using this technique, have subsequently been used further develop the tracking of population well-being and as a tool in developing health and related policies, as well as in planning and monitoring interventions, including in the identification of child malnutrition and child obesity, and are considered vital for the monitoring of the growth and health of children. Dr Borghi assessed these developments in 2020:

"*The WHO Child Growth Standards were adopted by more than 150 countries for assessing child growth and detect growth failure that leads to acute and chronic malnutrition, e.g. wasting, which in its severe version can lead to death and stunting, whose consequences include poor cognition and educational performance, low adult wages, lost productivity. Stunting, when accompanied by excessive weight gain later in childhood, an increased risk of nutrition-related chronic diseases in adult life. National Nutrition Surveillance systems in the majority of countries includes child growth assessment in periodical visits in health facilities and apply the WHO standards."* [S1]

The WHO Child Growth Standards are also used internationally not only to measure the relative successes of child nutrition and development programmes but also to identify health crises as they emerge. The 2020 joint report by UNICEF, WHO and the World Bank Group on the levels and trends in child malnutrition in all its forms (stunting, wasting or overweight) indicates that the global numbers of children under 5 suffering from stunting in 2019 is 144 million, and the report also identifies the emerging malnutrition issue of obesity, where the number of overweight children under 5 has risen to 38.3 million or 5.6% of the global population. Without metrics, including the WHO Child Growth Standards developed using Rigby and Stasinopoulos's GAMLSS methodology and software, assessment of programmes to address crises cannot be carried out. As the report states, in addition to long term nutrition programmes, "*regular data collection is critical to monitor and analyse country, regional and global progress*" towards addressing global child malnutrition. [S2]

In summarising the WHO Child Growth Standards' "*central role to, not only detect and treat children with acute malnutrition and to prevent [child] chronic malnutrition, but also it is the tool to*

ensure equity [and] to ensure we leave no one behind" [S1], Dr Borghi also notes Rigby and Stasinopoulos's *"indispensable contribution to the construction of the WHO Child Growth standards."* [S1]

Global Lung Function Initiative (GLI) The WHO reports that globally approximately 65 million people suffer from chronic obstructive pulmonary disease (COPD) and more than 339 million people are living with asthma. A major application of GAMLSS centile estimation methodology and software is the Global Lung Function Initiative's Quanjer GLI-2012 regression equations for spirometric indices. This initiative provides a global approach to monitoring lung function in growth and ageing. It uses GAMLSS to provide centiles for lung capacity (measured by total volume expelled, i.e. forced vital capacity, FVC) given the age, height, ethnic group and gender of the individual. '*GAMLSS (version 4.1-2) was used to derive the best fitting function of each outcome as a function of age and height in males and females'*, [S5, p1326]. The centiles are used to identify abnormally low lung capacity, potentially identifying lung disease (e.g. COPD or asthma), and initiate treatment.

Dr Sanja Stanojevic, the chair of the ERS Global Lung Function Initiative, stated that *"Within the field of respiratory medicine the application of the GAMLSS technique to develop all-age reference equations has had a tremendous impact in the field."* [S4] Spirometry is used in the clinical diagnosis of respiratory disease. A patient's spirometry test result is often an unrepeatable event and previous test results may not be available. The availability of a standardised reference set, in particular one that addresses ethnicity as well as physical attributes, allows the results to be assessed in context to provide a diagnosis. The GLI-2012 reference equations are currently endorsed *"by all of the 6 major respiratory societies and many national respiratory societies (including US, UK, Australia, Canada amongst many others)"* [S4]. The use of the GLI-2012 reference equations, utilising GAMLSS, has ensured that a standardised approach to respiratory function is available to researchers, healthcare professionals, and patients globally, while in Australia it is a requirement that a respiratory disease diagnosis is underpinned by a lung function test, and, as Dr Stanojevic reports, in *"Australia all lung function tests are interpreted using the GLI equations".* [S4]

Furthermore, she notes *"over 20 commercial pulmonary function companies have installed the equations in their equipment. The American Thoracic Society also recommends the GLI equations are the default equations for pulmonary function equipment."* [S4]. A global medical device and software company, with headquarters in the USA, Italy and France, Medical International Research (MIR) reported that: *'We have been using for many years the GLI equations in many spirometers and software that we produce and distribute everywhere in the world.. . .Spirometers and PC software for doctor use. PeakFlowMeters/Spirometers and Smartphone/Tablets' apps for self-care monitoring'* [S6]

The equipment and tools that use the GLI equations (derived using GAMLSS) provide more accurate diagnosis and hence better targeted treatment of lung conditions. *"Online tools including an API calculator that individuals can use and at last check more than 1 million individual results were analyzed, approximately 30 000 results are calculated using this tool alone every day."* [S4]. The use of the tools allows patients and practitioners to monitor lung function to manage the disease more effectively.

Paediatric Health Assessment A third major application of GAMLSS centile estimation methodology and software is in assessing and supporting paediatric health conditions. Hannelore Neuhauser and colleagues at the prestigious Robert Koch Institute, Germany's public health institute, obtained centiles for paediatric blood pressure given age and height, [S7 p7]. Dr. Neuhauser reports on the change to national health policy in Germany resulting from the use of GAMLSS to obtain the centiles: *"We have used GAMLSS for pediatric blood pressure percentiles which have been adopted in National Guidelines" since 2012* by *"the German Society of Pediatric Cardiology, the German Society of Paediatric Nephrology and the German Society of Pediatrics",* [S8]. Similarly, in China, GAMLSS has been used to obtain centiles for paediatric blood pressure given age and height, [S9] and [S10]. *"The reference curves of blood pressure by age and height*

were simultaneously fitted by using an extension of the LMS method, namely the generalized additive model for location scale and shape (GAMLSS) with the Box-Cox power exponential (BCPE) distribution or the Box-Cox t, fitted with GAMLSS 4.1-5", [S9, p2].

Correspondence from the Department of Clinical Epidemiology, Children's Hospital of Fudan University, China reports: *"By using R GAMLSS in our study, we published important papers and [created] important assessment tools for clinical use. Two examples are children blood pressure assessment and baby weight assessment for very preterm neonate babies'* [S10]. The preterm *'tool has been used in the in-hospital patients at Neonatal Intensive Care Unit of the Children's Hospital of Fudan University for over six years'* to 2020.[S10] to assess baby birth weight against gestational age for very preterm neonate babies. This allows the identification of babies with abnormally low birth weight given their gestational age, for whom medical intervention may be needed.

5. Sources to corroborate the impact (indicative maximum of 10 references)

S1. Testimonial letter from Dr. Elaine Borghi, World Health Organization, 20/07/2020
S2. United Nations Children's Fund (UNICEF), World Health Organization, International Bank for Reconstruction and Development/The World Bank. Levels and trends in child malnutrition: Key Findings of the 2020 Edition of the Joint Child Malnutrition Estimates. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO p2 & p15 https://www.who.int/publications/i/item/jme-2020-edition
S3. WHO Child Growth Standards: Methods and development: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. (2006) Geneva: World Health Organization
S4. Testimonial letter from Dr. Sanja Stanojevic, Chair of the European Respiratory Society (ERS) Global Lung Function Initiative, 19/01/2021
S5. Quanjer, P.H., Stanojevic, S., Cole, T.J., Baur, X., Hall, G.L., Culver, B.H., Enright, P.L., Hankinson, J.L., Ip, I.M.S.M. Zheng, J., Stocks, J. and the ERS Global Lung Function Initiative (2012) Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *European Respiratory Journal*, **40**, 1324-1343.
S6. Testimonial letter from Marco Fiaschini, Software Development Manager, Medical International Research, 20/12/2020
S7. Hannelore Neuhauser, Anja Schienkiewitz, Angelika Schaffrath Rosario, Reinhard Dortschy, Bärbel-Maria Kurth (2016) Reference percentiles for anthropometric measures and blood pressure based on the German Health Interview and Examination Survey for Children and Adolescents 2003–2006 (KiGGS). http://www.rki.de/EN/Content/Health_Monitoring/Health_Reporting/Contributions/beitraege_node.html
S8. Testimonial letter from Dr. Hannelore Neuhauser, Department of Epidemiology and Health Monitoring, Robert Koch Institute, 20/12/2020
S9. Yan, W., Liu, F., Wu, L., Zhang, Y. Zhou, W. and Huang, G. (2013) Blood pressure percentiles by age and height for non-overweight Chinese children and adolescents: analysis of the China health and nutrition surveys 1991-2009, *BMC Paediatrics*, **13**, 1-9.
S10. Testimonial letter from the Department of Clinical Epidemiology, Children's Hospital of Fudan University, Shanghai, China, 13/04/2020