Upscaling from African to global initiatives for child growth curves:

International Multicohort Pediatric Biomarker Collaboration (Biomarkers4Pediatrics) and Childhood Hypertension Consortium of South Africa (CHCSA)

Biomarkers4Pediatrics Collaboration

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INTRODUCTION

Rationale

- Monitoring child health using **objective indicators** crucial for
  - Clinical interventions
  - Identification of targets for public health prevention
  - Evaluation of Sustainable Development Goals

(https://sdgtestenvironment.github.io/sdg-indicators/en/)

- Existing reference values
  - Lacking consensus
  - Often only available for adult or Caucasian populations

Rationale

- Growing need for re-use and harmonization of data
  - To increase sample size
  - To take into account broad and diverse samples
  - To address gaps with regard to age-, sex- and ethnicity-specific reference values for biomarkers

➢ New pooling initiative **International Multicohort Pediatric Biomarker Collaboration (Biomarkers4Pediatrics)**

➢ Collaborating with the **Childhood Hypertension Consortium of South Africa (CHCSA)** and further

Aim

- To pool, harmonize and analyze data from pediatric populations
- In order to provide age-, sex- and ethnic-specific reference curves
  - On a global scale
  - For metabolic biomarkers
  - Covering the entire pediatric age range

➢ **To facilitate the diagnosis of metabolic syndrome early in life for clinical practice and public health**

Reference curves in IDEFICS/I.Family

- IDEFICS/I.Family pan-European multicenter cohort on child health
- **Ahrens et al. (2014)** proposed new definitions for metabolic syndrome (MetS) in children based on IDEFICS percentile curves

IDEFICS MetS-Score: $z_{WC} + z_{HOMA} + (z_{SBP}+z_{DBP})/2 + (z_{TRG} - z_{HDL})/2$

IDEFICS monitoring level:

- 3 of 4 markers > 90th percentile
  - Waist circumference
  - Blood pressure
  - HOMA insulin resistance or glucose
  - Triglycerides or HDL (<10th percentile)

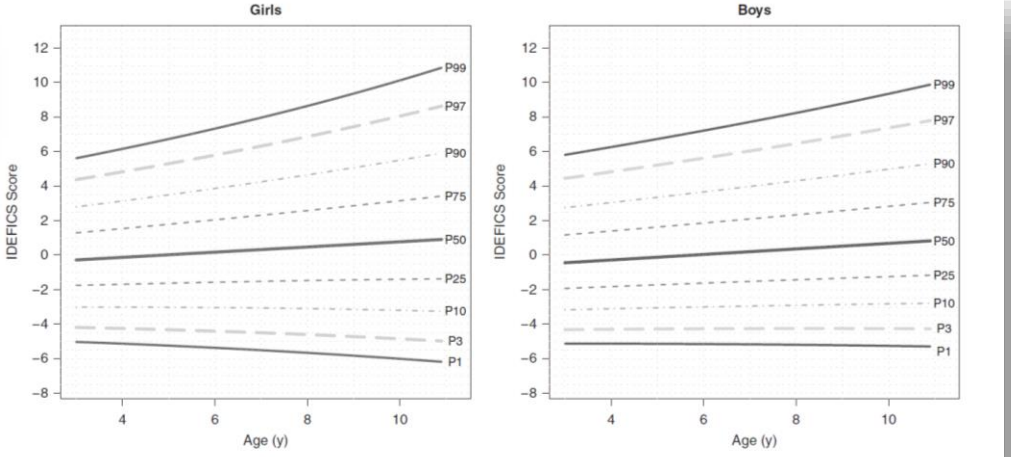

Figure 2. Age-specific percentiles of the IDEFICS metabolic syndrome score for girls (left) and boys (right). IDEFICS, Identification and prevention of Dietary- and lifestyle-induced health Effects in Children and infantS.

1. Ahrens et al. (2014) Metabolic syndrome in young children: definitions and results of the IDEFICS study. International Journal of Obesity. DOI: 10.1038/ijo.2014.130
2. Chiarelli & Mohn (2017) Early diagnosis of metabolic syndrome in children. Lancet Child Adolescent Health. DOI: 10.1016/S2352-4642(17)30043-3

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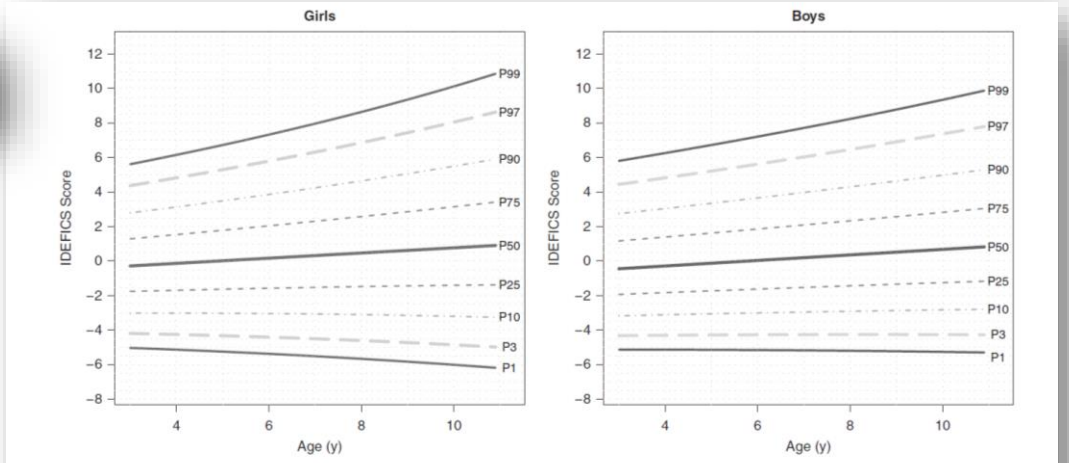
IDEFICS MetS-Score: $z_{WC} + z_{HOMA} + (z_{SBP}+z_{DBP})/2 + (z_{TRG} - z_{HDL})/2$

Definition recommended for worldwide use in pediatrics (**Chiarelli & Mohn, 2017**)



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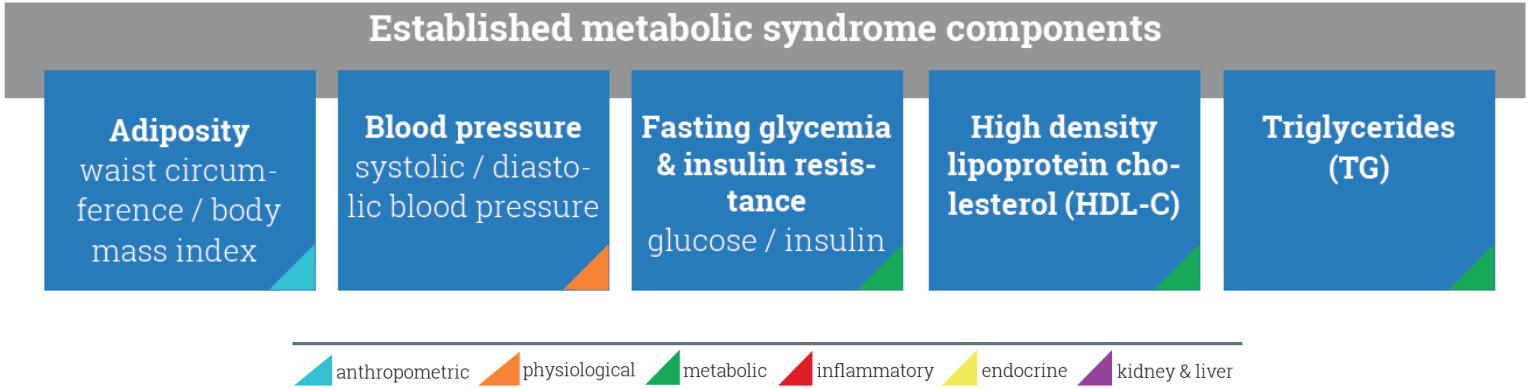
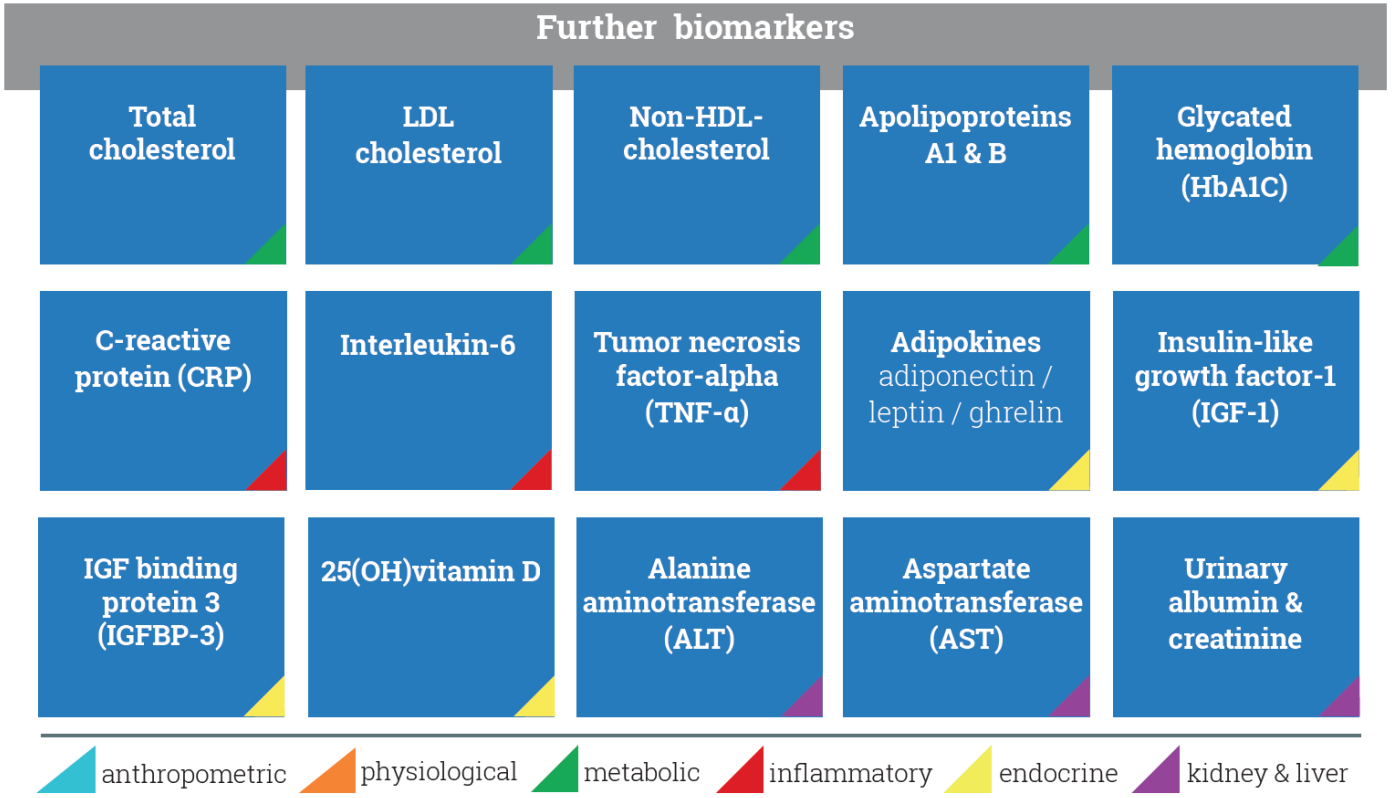
METHODS

Inclusion criteria

- Studies are eligible to participate if they meet the following criteria:
  - Epidemiological population-based studies (cross-sectional or cohort)
  - Participants‘ age range: 0 to <25 years
  - Relevant data available:



Additional biomarkers of interest



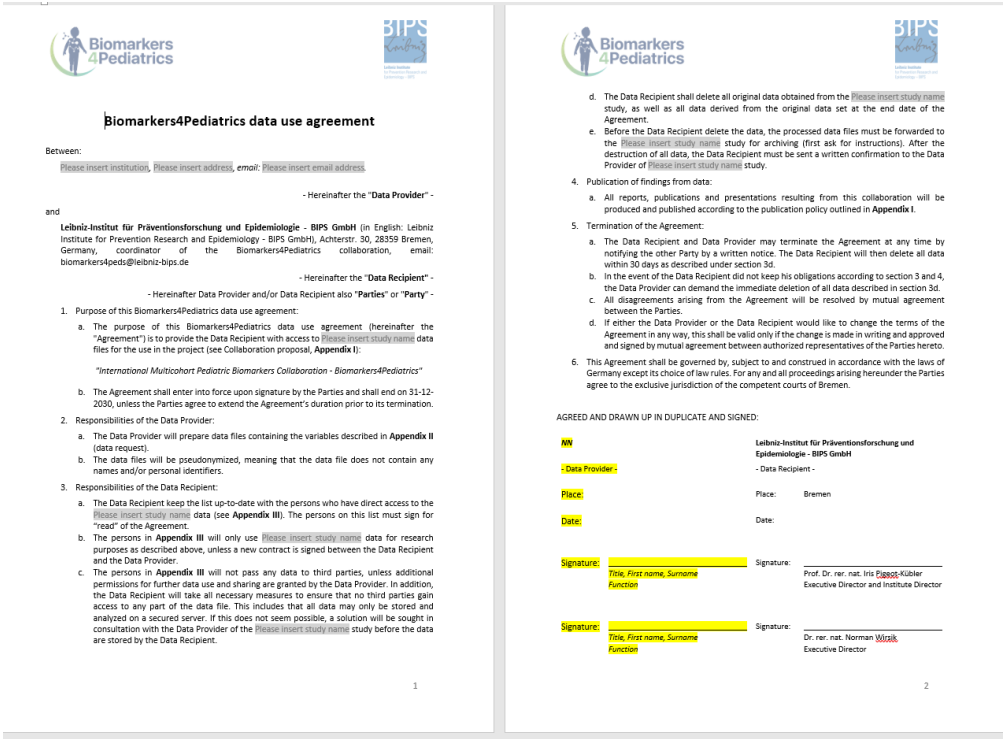
Inventory of eligible studies

Datenbank	Authors	Year	Continents	Countries	Period	Sample	age range; collection time points	Study name
MetS	Kushnir	2015	South America	Brazil	2013-2014	37.504	12-17 yrs	Study of Cardiovascular Risks
MetS	Zhu	2020	Asia	China	2013-2014	15.045	7-18 yrs	A national school-based healt
MetS	Weber	2014	North America	United States of America	2005-2006	13.018	1-19 yrs	C8 Health Project
MetS	Ahrens	2014	Europe	Europe	2007-2008	12.319	2-11 yrs	
MetS	Xu	2017	Asia	China	2007-2011	11.174	10-17 yrs	
MetS	Kelishadi	2006	Asia	Iran	2003-2004	4.811	6-18 yrs	Childhood and Adolescence Su
MetS	Ataie-Jafari	2014	Asia	Iran	2009-2010	4.641	10-18 yrs	Childhood and Adolescence Su
MetS	Warembourg	2021	Europe	UK, Spain, France, Greece	NR	4.279	4-5 yrs	HELIX: BIB (UK) , EDEN ((Franc
MetS	Ella	2010	Africa	Egypt	2004-2008	4.250	10-18 yrs	
MetS	Miller	2014	North America	United States of America	2001-2010	3.495	12-19 yrs	USNHANES 2001-2010
MetS	Mardones	2013	South America	Chile	2009-2011	3.325	10-15 yrs	
MetS	Ramirez-Velez	2017	South America	Colombia	2014-2015	2.877	9-17.9 yrs	Association for muscular stre
MetS	Chan	2014	Asia	Taiwan	2007-2009	2.727	12-16 yrs	Multilevel Risk Profiles for Ad
MetS	Rashidi	2014	Asia	Iran	2009-2011	2.246	10-19 yrs	
MetS	Seki	2009	South America	Brazil	2005	2.170	6-16 yrs	
MetS	Al-Husein	2014	Asia	Saudi Arabia	2003-2005	2.149	6-17 yrs	Saudi children's overweight, o
MetS	Gupta	2018	Asia	India	2015-2016	2.100	10-16 yrs	
MetS	Kerr	2021	Oceania	Australia	2004-	1.874	11-12 yrs	Longitudinal Study of Australi
MetS	Wang	2016	Asia	China	2013	1.770	7-17 yrs	
MetS	Zhao	2019	Asia	China	2017	1.766	10-15 yrs	Nutrition and Health Surveill
MetS	Rodriguez	2016	North America	USA	2005-2012	1.623	12-19 yrs	USNHANES 2005-2012
MetS	Kong	2008	Asia	Hong Kong	NR	1.616	14-15 yrs	
MetS	Park	2005	Asia	South Korea	1998	1.594	10-19 yrs	Korea National Health and Nu
MetS	Suarez-Ortegon	2012	South America	Colombia	2005	1.461	10-16 yrs	IFRECNTEC Study (identificati
MetS	Hosseinpanah	2013	Asia	Iran	NR	1.424	11-18 yrs	Tehran Lipid and Glucose Stud
MetS	Asghari	2017	Asia	Iran	NR	1.424	11-18 yrs	Tehran Lipid and Glucose Stud
MetS	Kim	2016	Asia	South Korea	2010-2012	1.420	10-18 yrs	Korea National Health and Nu
MetS	Saeed	2020	Asia	Yemen	2013	1.402	12-13 yrs	
MetS	Agirbasli	2006	Asia	Turkey	1992-1994	1.385	10-17 yrs	
MetS	Ostrihoňová	2017	Europe	Slovak Republic	2003-2012	1.294	10-17.99	
MetS	Serrano [Child]	2019	South America	Colombia	2006-2007	1.282	6-10 yrs	
MetS	Matsha	2009	Africa	South Africa	NR	1.272	10-16 yrs	
MetS	MacPherson	2016	North America	Canada	2007-2011	1.228	10-18 yrs	Canadian Health Measures Su
MetS	Reuter	2018	Asia	Brazil	2014-2015	1.200	12-17 yrs	BSchool Health - Phase III
MetS	Reina	2017	North America	USA	2012-2014	1.137	10-16 yrs	Hispanic Community Children'
MetS	Huang	2013	Oceania	Australia	2009	1.053	17 yrs	The Western Australian Pregn
MetS	Oliveira	2019	Asia	Brazil	NR	1.035	12-20 yrs	
MetS	Ahmadi	2020	Asia	Iran	2016-2017	1.035	6-18 yrs	
MetS	Mehairi	2013	Asia	United Arab Emirates	2010	1.018	12-18 yrs	
MetS	Fadzlina	2014	Asia	Malaysia	NR	1.014	13 yrs	Malaysian Health and Adolesc
MetS	Hirschler	2010	South America	Argentina	2007	1.009	6-14 yrs	
MetS	Vanlancker	2017	Europe	Europe	NR	1.004	12,5-17yrs	Healthy Lifestyle in Europe by
MetS	Benmohammed	2016	Africa	Algeria	2007	987	12-18 yrs	
MetS	Fernández-Aparicio	2020	Europe	Spain	NR	981	11-16 yrs	
MetS	Wang	2019	Europe	Spain	NR	976	10-15 yrs	
MetS	Rodriguez-Morán	2004	North America	Mexico	NR	965	10-18 yrs	
MetS	Khader	2010	Asia	Jordan	2009	937	7-18 yrs	
MetS	Rush	2016	Oceania	New Zealand	2014	931	14-15 yrs	Pacific Islands Families
MetS	Andaki	2018	South America	Brazil	2011-2012	929	6-10 yrs	
MetS	Elfaki	2022	Africa	Sudan	2018-2019	921	10-15 yrs	
MetS	Villalobos Reyes	2014	South America	Venezuela	2010-2011	916	9-18 yrs	CREDEFAR Study
MetS	Daly	2005	Oceania	New Zealand	NR	855	14-18 yrs	
MetS	Agudelo	2014	South America	Colombia	2010-2012	851	10- 18 yrs	
MetS	Ong	2023	Asia	Singapore	2009-2010	839	6 years	Growing Up in Singapore Tow
MetS	Song	2017	Asia	China	2009	831	7-18 yrs	China Health and Nutrition Su
MetS	Ramirez-Silva	2015	North America	Mexico	2009-2011	727	4 yrs	Prenatal Omega-3 Fatty Acid S
MetS	Burrows	2015	South America	Chile	NR	667	16-17 yrs	
MetS	Hong	2012	Asia	Vietnam	2007	617	13-16 yrs	
MetS	Haroun	2018	Asia	United Arab Emirates	2014	596	10-15,9 yrs	
MetS	Matsushita	2015	Asia	Japan	2010-2012	585	4,5-12,75 yrs	
MetS	Pitangueira	2014	Asia	Brazil	2006	540	7-14 yrs	
MetS	Bahrani	2016	Asia	Iran	NR	538	14-18 yrs	
MetS	Suarez-Ortegon	2016	South America	Colombia	NR	494	5-9 yrs	IFRECNTEC Study (identificati
MetS	Aghbar	2019	Asia	Palestine	NR	487	6-18 yrs	
MetS	Al-Isa	2010	Asia	Kuwait	2008	431	10-19yrs	
MetS	Chedid	2009	Asia	Lebanon	NR	381	18-30 yrs	
MetS	Galera-Martínez	2015	Europe	Spain	NR	379	12-16.9 yrs	
MetS	Sekokotla	2017	Africa	South Africa	NR	371	13-18 yrs	
MetS	Wibaek	2019	Africa	Ethiopia	2008-2012	340	5 years	Ethiopian Infant Anthropome
MetS	Valery	2009	Oceania	Australia	NR	158	5-17 yrs	

- $N_{study-specific}$ = 340 - 37,500 children
- $N_{overall}$ = 300,000 children
- Period: 1991-2019
- **All continents covered: 97 studies**
  - Africa: 6
  - Asia: 35
  - Europe: 27
  - North America: 9
  - Oceania: 8
  - South America: 12

Study recruitment – preparatory work

- Biomarkers4Pediatrics website:
  - www.biomarkers4pediatrics.eu
- Recruitment documents
  - B4P FactSheet
  - B4P Data Use Agreement
  - B4P Data Collection Sheet (extract meta data information)
    - General study information
    - Variable availability
    - Extended data dictionairy



Biomarkers4Pediatrics data use agreement

Between:

Please insert institution, Please insert address, *email*: Please insert email address.

- Hereinafter the "**Data Provider**" -

and

Leibniz-Institut für Präventionsforschung und Epidemiologie - BIPS GmbH (in English: Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH), Achterstr. 30, 28359 Bremen, Germany, coordinator of the Biomarkers4Pediatrics collaboration, email: biomarkers4peds@leibniz-bips.de

- Hereinafter the "**Data Recipient**" -

- Hereinafter Data Provider and/or Data Recipient also "**Parties**" or "**Party**" -

1. Purpose of this Biomarkers4Pediatrics data use agreement:
   a. The purpose of this Biomarkers4Pediatrics data use agreement (hereinafter the "Agreement") is to provide the Data Recipient with access to Please insert study name data files for the use in the project (see Collaboration proposal, **Appendix I**):

      "International Multicohort Pediatric Biomarkers Collaboration - Biomarkers4Pediatrics"

   b. The Agreement shall enter into force upon signature by the Parties and shall end on 31-12-2030, unless the Parties agree to extend the Agreement's duration prior to its termination.
2. Responsibilities of the Data Provider:
   a. The Data Provider will prepare data files containing the variables described in **Appendix II** (data request).
   b. The data files will be pseudonymized, meaning that the data file does not contain any names and/or personal identifiers.
3. Responsibilities of the Data Recipient:
   a. The Data Recipient keep the list up-to-date with the persons who have direct access to the Please insert study name data (see **Appendix III**). The persons on this list must sign for "read" of the Agreement.
   b. The persons in **Appendix III** will only use Please insert study name data for research purposes as described above, unless a new contract is signed between the Data Recipient and the Data Provider.
   c. The persons in **Appendix III** will not pass any data to third parties, unless additional permissions for further data use and sharing are granted by the Data Provider. In addition, the Data Recipient will take all necessary measures to ensure that no third parties gain access to any part of the data file. This includes that all data may only be stored and analyzed on a secured server. If this does not seem possible, a solution will be sought in consultation with the Data Provider of the Please insert study name study before the data are stored by the Data Recipient.

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   d. The Data Recipient shall delete all original data obtained from the Please insert study name study, as well as all data derived from the original data set at the end date of the Agreement.
   e. Before the Data Recipient delete the data, the processed data files must be forwarded to the Please insert study name study for archiving (first ask for instructions). After the destruction of all data, the Data Recipient must be sent a written confirmation to the Data Provider of Please insert study name study.
4. Publication of findings from data:
   a. All reports, publications and presentations resulting from this collaboration will be produced and published according to the publication policy outlined in **Appendix I**.
5. Termination of the Agreement:
   a. The Data Recipient and Data Provider may terminate the Agreement at any time by notifying the other Party by a written notice. The Data Recipient will then delete all data within 30 days as described under section 3d.
   b. In the event of the Data Recipient did not keep his obligations according to section 3 and 4, the Data Provider can demand the immediate deletion of all data described in section 3d.
   c. All disagreements arising from the Agreement will be resolved by mutual agreement between the Parties.
   d. If either the Data Provider or the Data Recipient would like to change the terms of the Agreement in any way, this shall be valid only if the change is made in writing and approved and signed by mutual agreement between authorized representatives of the Parties hereto.
6. This Agreement shall be governed by, subject to and construed in accordance with the laws of Germany except its choice of law rules. For any and all proceedings arising hereunder the Parties agree to the exclusive jurisdiction of the competent courts of Bremen.

AGREED AND DRAWN UP IN DUPLICATE AND SIGNED:

NN	**Leibniz-Institut für Präventionsforschung und Epidemiologie - BIPS GmbH**
- Data Provider -	- Data Recipient -
Place:	Place: Bremen
Date:	Date:
Signature: _____	Signature: _____
Title, First name, Surname	Prof. Dr. rer. nat. Iris Pigeot-Kübler
Function	Executive Director and Institute Director
Signature: _____	Signature: _____
Title, First name, Surname	Dr. rer. nat. Norman Wirzik
Function	Executive Director

2

Study recruitment – preparatory work

- Set up federated analysis infrastructure if data cannot be shared physically
- Allows privacy preserving data access using DataSHIELD[3]
- Algorithm developed and tested for **generalized additive models for location, scale and shape (GAMLSS)**[4] to derive percentile curves in federated setting

3. Wilson et al. (2017) DataSHIELD - New directions and dimensions. DOI: 10.5334/dsj-2017-021
4. Stasinopoulos and Rigby (2007) Generalized additive models for location scale and shape (GAMLSS) in R. DOI: 10.1111/j.1467-9876.2005.00510.x

Study recruitment – initial phase

- Principal investigators from previous collaborations contacted, e.g.,
  - HELENA study (ESP, Luis A. Moreno*)
  - ABCD study (NL, Tanja Vrijkotte**)
- **Documents exchanged with CHCSA/Ruan Kruger*****
  - Suitable studies are mutually informed about both initiatives

➢ Valuable inputs and experiences

  - Fine-tuning of documents and approaches

* Growth Exercise, Nutrition and Development Research Group, Instituto Agroalimentario de Aragón,Instituto de Investigación Sanitaria Aragón, Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y Nutrición, University of Zaragoza, Spain

** Department of Public and Occupational Health, Amsterdam University Medical Center (Amsterdam UMC), University of Amsterdam, The Netherlands

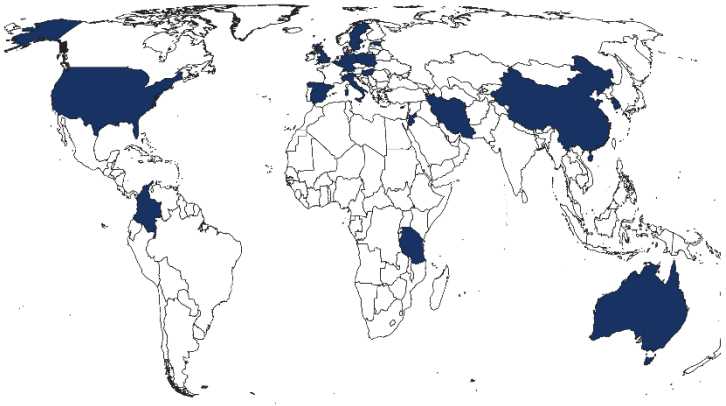
*** Hypertension in Africa Research Team/SAMRC Research Unit for Hypertension and Cardiovascular Disease, North-West University, Potchefstroom, South Africa

Study recruitment – main phase

- Contacting studies
- Signing data use agreements
- Filling meta data extraction sheets
- Providing / receiving data
- Integrating study data in data snapshots
- ➢ **First snapshot available**

Preliminary Results

Recruitment status



	Countries	Studies	N (obs.)
Received data	18	12	~202.000
Integrated data in 1st snapshot	14	8	92.732*

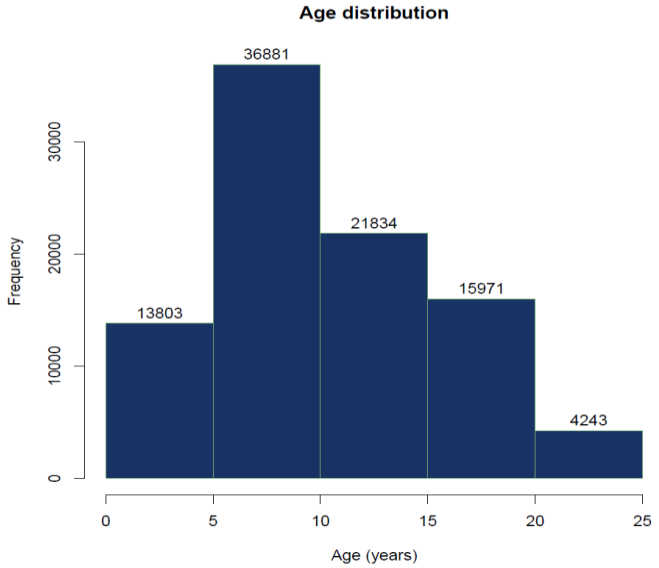
*blood biomarker available

- White spots in Africa and South America
- Collaboration with several studies in preparation

1st snapshot results

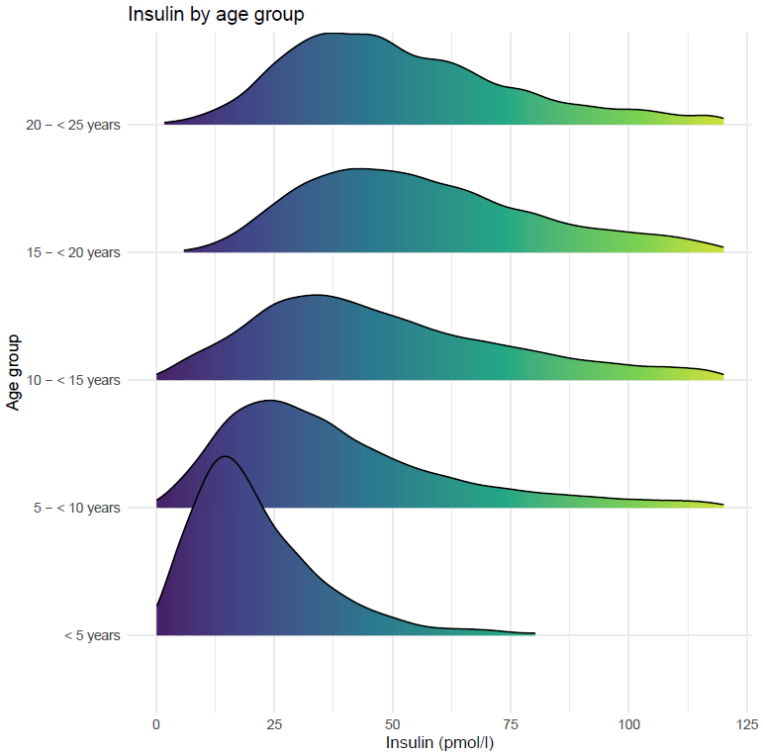
- Includes ALSPAC[5,6], CASPIAN, CHNS, DEGS[7], IDEFICS/I.Family[8], KIGSS[9,10], LSAC[11], and ZUTAS[12]
- Balanced sex ratio but unbalanced age distribution

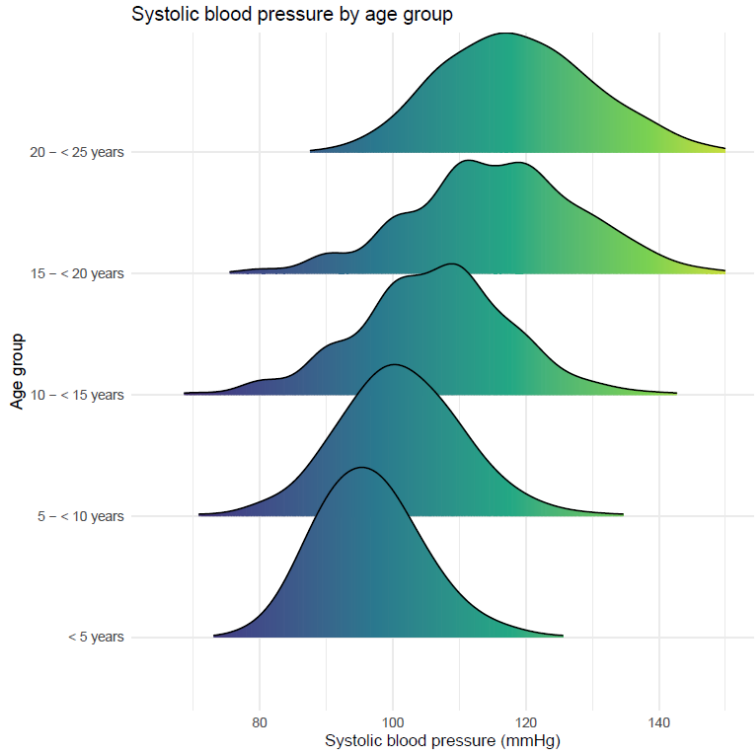
Sex	N
Male	46.557
Female	46.175



1st snapshot results

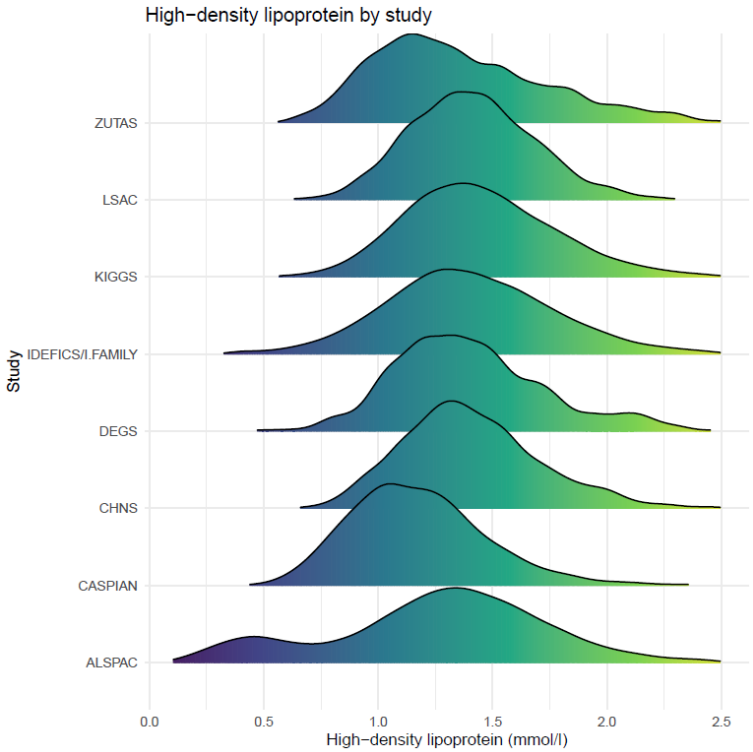
Biomarker distributions differ strongly by age

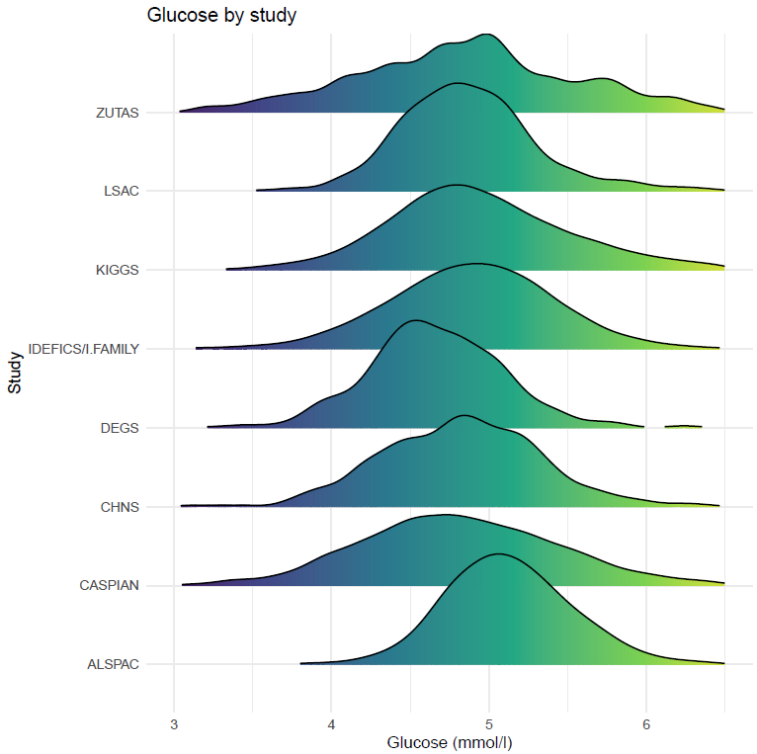




1st snapshot results

Biomarker distributions differ by study





Outlook

Outlook

- **Biomarkers4Pediatrics pools child biomarker data from multiple studies worldwide**
- **Synergies with CHCSA**
- Deep, harmonized data set offers opportunities for further investigations
  - Challenges: harmonization and modeling
- Data sharing & joint use of harmonized data will pave the way towards closing the gap in pediatric epidemiology and advancement of pediatric health research globally

(Study) References

1. Ahrens W et al. (2014) Metabolic syndrome in young children: definitions and results of the IDEFICS study. DOI: 10.1038/ijo.2014.130
2. Chiarelli F and Mohn, A (2017) Early diagnosis of metabolic syndrome in children. DOI: 10.1016/S2352-4642(17)30043-3
3. Wilson R et al. (2017) DataSHIELD - New directions and dimensions. DOI: 10.5334/dsj-2017-021
4. Stasinopoulos DM and Rigby RA (2007) Generalized additive models for location scale and shape (GAMLSS) in R. DOI: 10.1111/j.1467-9876.2005.00510.x
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Biomarkers 4Pediatrics

www.biomarkers4pediatrics.eu

Further studies are welcome!

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