Advances in Predictive, Preventive and Personalised Medicine
Series Editor: Olga Golubnitschaja

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Flammer Syndrome

From Phenotype to Associated Pathologies, Prediction, Prevention and Personalisation

EPMA European Association for Predictive Preventive & Personalised Medicine

Springer

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What This Book Series Is About…

Current Healthcare: What Is Behind the Issue?

For many acute and chronic disorders, the current healthcare outcomes are considered as being inadequate: global figures cry for preventive measures and personalised treatments. In fact, severe chronic pathologies such as cardiovascular disorders, diabetes and cancer are treated after onset of the disease, frequently at near end-stages. Pessimistic prognosis considers pandemic scenario for type 2 diabetes mellitus, neurodegenerative disorders and some types of cancer over the next 10–20 years followed by the economic disaster of healthcare systems in a global scale.

Advanced Healthcare Tailored to the Person: What Is Beyond the Issue?

Advanced healthcare promotes the paradigm change from delayed interventional to predictive medicine tailored to the person, from reactive to preventive medicine and from disease to wellness. The innovative predictive, preventive and personalised medicine (PPPM) is emerging as the focal point of efforts in healthcare aimed at curbing the prevalence of both communicable and non-communicable diseases such as diabetes, cardiovascular diseases, chronic respiratory diseases, cancer and dental pathologies. The cost-effective management of diseases and the critical role of PPPM in modernisation of healthcare have been acknowledged as priorities by global and regional organisations and health-related institutions such as the Organisation of the United Nations, the European Union and the National Institutes of Health.

Why Integrative Medical Approach by PPPM as the Medicine of the Future?

PPPM is the new integrative concept in healthcare sector that enables to predict individual predisposition before onset of the disease, to provide targeted preventive measures and create personalised treatment algorithms tailored to the person. The expected outcomes are conducive to more effective population screening, prevention early in childhood, identification of persons at risk, stratification of patients for the optimal therapy planning and prediction and reduction of adverse drug-drug or drug-disease interactions relying on emerging technologies, such as pharmacogenetics, pathology-specific molecular patterns, subcellular/cellular imaging, disease modelling, individual patient profiles, etc. Integrative approach by PPPM is considered as the medicine of the future. Being at the forefront of the global efforts, the European Association for Predictive, Preventive and Personalised Medicine (EPMA, http://www.epmanet.eu/) promotes the integrative concept of PPPM among healthcare stakeholders, governmental institutions, educators, funding bodies and patient organisations and in the public domain.

The current book series, published by Springer in collaboration with EPMA, overviews multidisciplinary aspects of advanced biomedical/medical approaches and innovative technologies. Integration of individual professional groups into the overall concept of PPPM is a particular advantage of this book series. Expert recommendations focus on the cost-effective management tailored to the person in health and disease. Innovative strategies are considered for standardisation of healthcare services. New guidelines are proposed for medical ethics, treatment of rare diseases, innovative approaches to early and predictive diagnostics, patient stratification and targeted prevention in healthy individuals, persons at risk, individual patient groups, subpopulations/populations, institutions, healthcare economy and marketing.

Bonn, Germany Olga Golubnitschaja

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About the Book Series Editor

Prof. Dr. Olga Golubnitschaja Department of Radiology, Medical Faculty of Rheinische Friedrich-Wilhelms-University in Bonn, Germany, has studied journalism, biotechnology and medicine and has been awarded research fellowships in Austria, Russia, UK, Germany, the Netherlands and Switzerland (early and predictive diagnostics in paediatrics, neurosciences and cancer). Dr. Golubnitschaja is the author of more than 400 well-cited international publications (research and review articles, position papers, books and book contributions) in the innovative field of predictive, preventive and personalised medicine (PPPM) with the main research focussing on pre- and perinatal diagnostics, diagnostics of cardiovascular disease and neurodegenerative pathologies and predictive diagnostics in cancer and diabetes.

Dr. Golubnitschaja was awarded National and International Fellowship of the Alexander von Humboldt-Foundation, Highest Prize in Medicine and Eiselsberg Prize in Austria.

Since 2009, Dr. Golubnitschaja is the Secretary-General of the "European Association for Predictive, Preventive and Personalised Medicine" (EPMA, Brussels) networking over 50 countries worldwide, www.epmanet.eu; Book Series Editor of *Advances in Predictive, Preventive and Personalised Medicine*, Springer Nature; Book Editor of *Predictive Diagnostics and Personalised Treatment: Dream or Reality*, Nova Science Publishers, New York 2009; Book Co-editor *Personalisierte Medizin*, Health Academy, Dresden 2010.

Dr. Golubnitschaja is the European Representative in the EDR-Network at the National Institutes of Health, USA, http://edrn.nci.nih.gov/.

Dr. Golubnitschaja is a Regular Reviewer for over 30 clinical and scientific journals and serves as a Grant Reviewer for the national (Ministries of Health in several European countries) and international funding bodies.

Since 2007 until the present, she works as the European Commission evaluation expert for FP7, Horizon 2020, IMI-1 (Innovative Medical Initiatives) and IMI-2. In years 2010–2013, she was involved in creating the PPPM-related contents of the European Programme "Horizon 2020".

Currently, Dr. Golubnitschaja is the Vice-Chair of the Evaluation Panel for Marie Curie Mobility Actions at the European Commission in Brussels.

Flammer Syndrome in the Global Context – The "U-Shape" of Health Risks

Olga Golubnitschaja

Abstract Unmet healthcare needs of young populations are the key issue of currently observed epidemics of non-communicable disorders. Moreover, an unprecedented decrease in the average age of onset of these disorders is recorded. The majority of non-communicable disorders carry a chronic character by progressing over a couple of years from a reversible suboptimal health condition to irreversible pathology with collateral complications. The time-frame between both conditions is the operational area for predictive diagnosis and identification of persons at risk by innovative screening programmes followed by the most cost-effective personalised treatment possible, namely primary prevention tailored to the person. Particularly in young people, both abnormally low and high BMI play an important role with long-term adverse health effects. Monitoring both underweight and overweight trends across the European countries and worldwide using data objectively measured and obtained with comparable methods, thoroughly performed analysis of the trends causality as well as follow-up mitigating programmes are essential measures which should be considered a public health priority.

In contrast to the overweight subpopulations, the causality, risks and associated pathologies linked to the underweight subpopulations are much less understood. Actual studies clearly demonstrate that thinness is an overlooked phenomenon with wide variation in prevalence and trends across developed countries. The matter deserves longitudinal studies in multinational context to understand risk factors and to contribute to targeted preventive programmes focused on thinness and follow-up. The causality is complex. The book highlights the most recent knowledge collected in the

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area providing facts and hypothesis for the follow-up investigations. Flammer syndrome phenotype typical for young slim persons is in the focus providing insights into characteristic symptoms and deficits functionally liked to mechanisms which may underlie the development of associated pathologies. Corresponding health-threating conditions are exemplified in the book utilising an up-to-date multi-professional expertise considering cardiovascular, ophthalmologic, neurologic, psychologic, psychiatric, gynaecologic, otorhinolaryngologic, dental and nutritional aspects, several syndromes, disordered eating, eating disorders, microbiome, sleep medicine, wound healing, and application of innovative technologies, amongst others.

Keywords Flammer syndrome · BMI · Overweight · Underweight · Health risks · Major pathologies · Non-communicable diseases · Cardiovascular · Cancer · Mental behavioural disorder · Respiratory diseases · Epidemic · Teenager age · Adolescence · Predictive preventive personalised medicine · Phenotyping · Genotyping · Multilevel diagnostics · Strategy · Ophthalmology · Neurology · Psychology · Psychiatry · Gynaecology · Oncology · Otorhinolaryngology · Dentistry · Nutrition · Disordered eating · Eating disorders · Microbiome · Sleep medicine · Wound healing · Innovative technologies · Paradigm change · Holistic approach · Health economy · European platform

1 Unmet Healthcare Needs of Young Populations Is the Key Issue of the "Reactive" Medicine: The Paradigm Shift to PPPM Is Crucial

Unmet healthcare needs of young populations is the key issue of currently observed epidemics of non-communicable disorders. Moreover, an unprecedented decrease in the average age of onset of these disorders is recorded as characteristic for the early twenty-first century: teenagers diseased on diabetes type 2, depression and suicide in youth, frequent vascular dysregulation and "young" strokes with unknown aetiology, reproductive dysfunction, aggressive mestastasing cancer subtypes in 20+ years old patients with particularly poor outcomes, significantly increasing prevalence of preventable high myopia in high school students, in young people – increasing prevalence of impaired wound healing, allergic reactions and autoimmunity as well as respiratory disorders, amongst others [1–11].

Paradox is that specifically in adolescents the adverse health effects by suboptimal health conditions are reversible in most cases. This unique capacity is, however, not adequately utilised by current concepts of healthcare: still the clinical manifestation of the disease is the acknowledged indicator for conventional medical services. However, the majority of non-communicable disorders carry a chronic character by progressing over a couple of years from a reversible suboptimal health condition to irreversible pathology with collateral complications. The time-frame between both conditions is the operational area for predictive diagnosis and identification of persons at risk by innovative screening programmes followed by the most cost-effective personalised treatment possible, namely primary prevention tailored to the person.

2 Opposed Trends in Adolescents

Specifically in adolescents, physical and mental health linked to the body shape plays the central role for major aspects in their life such as optimal health condition, sexual life and long-term partnering, successful career development as discussed in the chapter 3 "Flammer syndrome-affected individuals are predisposed to associated pathologies early in life: Psychological and psychiatric aspects". However, complex and challenging educational efforts, much time spent with computer, due to unavoidable computerisation of a daily life, amongst others, strongly promote sedentary life-style resulting in physical inactivity, overweight, obesity, and early diabetes type 2 with a cascade of collateral pathologies. For example, in Germany in average from 100 teenagers aged 12–16 years, 11 are overweight and 9 obese. Similar statistics are recorded for many European countries as well as worldwide [12, 13].

On the other hand, recognition of this actuality gave rise to the opposed trends: 50% of female teenagers and 25% of male teenagers with normal weight in Germany believe that they are overweight and start unsupervised dieting early in life. Consequently, "disordered eating" followed by clinical manifestation of eating and mental disorders in adolescence such as anorexia nervosa and depression become highly prevalent in young populations. Table 1 summarises global statistics for the prevalence of abnormal body-weight; risks associated with both trends are listed [12–16].

3 Association Between Abnormal Weight and Increased Mortality: The "U-Shape" of Risks

A potential association of the abnormal BMI and increased risks to die from one of the most common pathologies has been recently analysed by a large-scale population-based cohort study which considered 3.6 million adults in the UK [17]. The results are well in consensus with our consideration of both – overweight and underweight subpopulations as particularly risky for increased pathology incidence and mortality rates. Figure 1 graphically summarises clear "U-shape" trends in association between the all-case mortality risks and corresponding BMI values. Noteworthy, with very few exceptions, the lowest risks have been demonstrated by 22–25 kg/m^2 for the absolute majority of pathologies considered [17]. Noteworthy, smoking as otherwise considered a strong risk factor has rather minor influence on the BMI/all-case mortality association. Finally, depending on the type of pathology, either right wing (low BMI, e.g. neurological dementia and mental/behavioural cause of death) or left one (high BMI, e.g. hypertensive heart disease as the cause of death) or both – low and high BMI equally (e.g. respiratory disease as the cause of death) might be particularly risky for the affected person. Even accidental death – both transport-related and non-related ones demonstrate the "U-shape" with low and high BMI as risky for an increased mortality.