Comparing stigmatization and perceived mental stress

following COVID-19 AND/OR in mental health disorders

- a psychoimmunological approach

(STIGMA-STRESS-IMMUN)

Principal investigator (PI)

Assoc. Prof. Dr. Katharina Hüfner

Department of Psychiatry, Psychotherapy and Psychosomatics

Division of Psychiatry II

Medical University Innsbruck

Anichstr. 35

6020 Innsbruck

Co-PI

Prof. Dr. Alex Hofer

Department of Psychiatry, Psychotherapy and Psychosomatics

Division of Psychiatry I

Medical University Innsbruck0

Anichstr. 35

6020 Innsbruck

Study sites

Medical University Innsbruck and Tirol Kliniken GmbH, Department of Psychiatry, Psychotherapy and Psychosomatics, Divisions of Psychiatry I and II

Bezirkskrankenhaus Kufstein, Division of Psychiatry

Krankenhaus St. Vinzenz, Zams, Division of Psychiatry and Psychotherapeutic Medicine

Project partners

*Medical Director at Tirol Kliniken GmbH*

Dr. Alexandra Kofler

*Medical University Innsbruck, Institute for Legal Medicine and Core Facility Metabolomics*

Assoc. Prof. Dr. Herbert Oberacher

*Medical University Innsbruck, Institute for Biological Chemistry*

Prof. Dr. Dietmar Fuchs

*Medical University Innsbruck, Institute for Medical Biochemistry*

Assoc. Prof. Dr. Johanna Gostner

Cooperating Institutions

*Bezirkskrankenhaus Kufstein, Division of Psychiatry*

Assoc. Prof. Dr. C. Miller (Head of Division)

Dr. Johann Margreiter (physician)

*Krankenhaus St. Vinzenz, Zams, Division of Psychiatry and Psychotherapeutic Medicine*

Assoc. Prof. Dr. Martin Kurz (Head of Division)

Dr. Arnold Schiechtl (physician)

*Medical Directors at Bezirkskrankenhaus Kufstein and Krankenhaus Zams*

Assoc. Prof. Dr. C. Miller

Assoc. Prof. Dr. Eduard Wöll

**Content**

[1. Scientific Background and Hypothesis 2](#_Toc69225033)

[1.1. Overall study rational 2](#_Toc69225034)

[1.2. Research aim and questions 3](#_Toc69225035)

[1.3. Innovation 6](#_Toc69225036)

[1.4. International research up to date 6](#_Toc69225037)

[1.4.1. Stigmatization due to COVID-19 6](#_Toc69225038)

[1.4.2. Experiences from the SARS epidemic 7](#_Toc69225039)

[1.4.3. Stigmatization due to mental health disorder 7](#_Toc69225040)

[1.4.4. Stigmatization and mental stress 7](#_Toc69225041)

[1.4.5. The concept of resilience 8](#_Toc69225042)

[1.4.6. Psychoimmunological aspects of mental stress and psychiatric disorders 8](#_Toc69225043)

[1.4.7. Own research in the field 9](#_Toc69225044)

[2. Study design 9](#_Toc69225045)

[2.1. Type of Study 9](#_Toc69225046)

[2.2. Planned interventions 9](#_Toc69225047)

[2.3. Sample description and data collection 10](#_Toc69225048)

[2.4. Primary and secondary endpoints 11](#_Toc69225049)

[2.5. Risk assessment 11](#_Toc69225050)

[2.6. Statistics / Sample size 11](#_Toc69225051)

[2.7. Methods used for bias reduction 12](#_Toc69225052)

[2.8. Assessment battery 12](#_Toc69225053)

[2.9. Availability of patients, recruiting 14](#_Toc69225054)

[2.10. Psychoimmunological analyses (study part B) 14](#_Toc69225055)

[2.10.1. Blood draw 14](#_Toc69225056)

[2.10.2. Metabolomics 14](#_Toc69225057)

[2.10.3. Cytokines 14](#_Toc69225058)

[2.10.4. Neurotransmitter precursor amino acids and related biogenic amines 15](#_Toc69225059)

[2.10.5. Cortisol and other steroid hormones and immunomodulatory metabolites 15](#_Toc69225060)

[2.10.6. SARS-CoV-2 Antibodies 15](#_Toc69225061)

[2.11. Gender Aspects 15](#_Toc69225062)

[2.12. Cooperations 15](#_Toc69225063)

[2.13. Work Packages and Timeline 15](#_Toc69225064)

[3. Ethical and judicial principles 16](#_Toc69225065)

[3.1 Information and informed consent 16](#_Toc69225066)

[3.2. Conflict of interest 17](#_Toc69225067)

[3.3. Data Handling 17](#_Toc69225068)

[4. Human Resources 17](#_Toc69225069)

[4.1. Involved researchers 17](#_Toc69225070)

[4.2. Career development 19](#_Toc69225071)

[5. Abbreviations 20](#_Toc69225072)

[Appendix 1 21](#_Toc69225073)

[Appendix 1. a. Details on the research institution 21](#_Toc69225074)

[Appendix 1. b. Information on requested funding 23](#_Toc69225075)

[Appendix 2: Summary of the clinical study 25](#_Toc69225076)

[Appendix 3: References 28](#_Toc69225077)

[Appendix 4 Curriculum vitae 33](#_Toc69225078)

# Scientific Background and Hypothesis

This section in brief: Several of the world´s leaders and much acclaimed scientist have called for scientific evidence on stigmatization during the COVID-19 pandemic, but rigorous and large scale data are still scarce. But only if we recognize the type, extent, and psychoimmunological consequences of stigmatization and the therefrom resulting mental stress, will it be possible to develop targeted programs to reduce them (also discussed at World Economic Forum). Since such initiatives for improving mental health will involve allocating substantial financial resources, rigorous scientific data are essential.

In the present prospective longitudinal study we will investigate stigmatization, mental stress as well as mental and physical health in 4 groups: healthy individuals (SC2-MI-), individuals following COVID-19 (not in acute phase of disease) without a mental illness (SC2+MI-), individuals living with a mental illness who have not been tested positive for SARS-CoV-2 (SC2-MI+) as well as individuals with dual diagnosis (SC2+MI+). Mental stress is immunomodulatory which is one of the basic concepts of psychoimmunology. Psychoimmmunological mechanisms linking mental and physical disease in a bi-directional relationship will be explored with special focus on the role of stigmatization in the process. Psychoimmunology might also be the pathophysiology mediating some or all symptoms of the long COVID/post COVID syndrome which is known to consist of a combination of mental and physical symptoms.

## 1.1. Overall study rational

The research objectives are to

(A) assess stigmatization and mental stress in 4 groups: healthy individuals (SC2-MI-), individuals following COVID-19 (not in acute phase of disease) without mental illness (SC2+MI-), individuals living with a mental illness who have not been tested positive for SARS-CoV-2 (SC2-MI+) as well as individuals with dual diagnosis (SC2+MI+)

(B) explore the underlying psychoimmunological mechanisms.

Stigmatization and the resulting discrimination are a major cause of distress in affected individuals, thereby causing mental and physical disease or impeding recovery therefrom (Link et al., 2001). Psychoimmunological mechanisms are assumed to underly this association: mental stress-induced alterations in an individual´s immunometabolic signature leading to physical and/or mental disease (bi-directional relationship), and overall reduced quality of life (Hüfner et al. 2015a, 2019, 2020a). Psychoimmunological mechanisms, especially the persistence of an activated immune system, might also mediate some or all symptoms of the long COVID/post COVID syndrome which is known to consist of a combination of mental and physical symptoms (Huang et al. 2021). For the medical health care system and the Austrian society as a whole, it is important to have these data collected locally since stigmatization differs between cultures, societies and countries. The data collected in this COVID-19-related research project will be important far beyond the current crisis: we will investigate basic biomedical concepts of the associations between stigmatization, mental stress and physical and mental disease. This knowledge will essentially help legitimate and support existing and “post-COVID world” mental health programs which are advocated also by leading experts on the World Economic Forum (see https://www.weforum.org/events/the-davos-agenda-2021/themes/healthy-futures).

## 1.2. Research aim and questions

This is a prospective longitudinal cohort study with two points of data collection 6 months apart. The project has two parts: study part A focusses on assessing stigmatization and mental stress during the COVID-19 pandemic in healthy individuals (SC2-MI-), individuals following a COVID-19 (not in acute phase of disease) without mental illness (SC2+MI-), individuals living with a mental illness who have not been tested positive for SARS-CoV-2 (SC2-MI+) as well as individuals with dual diagnosis (SC2+MI+). The prevalence of symptoms of anxiety and depression as well as quality of life and resilience will be investigated together with parameters of physical health (with special focus on disease severity and residual COVID-19 symptoms) in this online part of the study. In study part B we will assess focus on the psychoimmunological mechanisms linking physical and mental health. This is very important since immunological alterations related to mental stress can predispose individuals towards infectious diseases such as COVID-19 and on the other hand are associated with mental disorders such as depressive symptoms (bi-directional relationship between mental and somatic disorders mediated by psychoimmunogical mechanisms). Preliminary work: An early start of the study was of utmost importance to be able to fully explore the reach and consequences of the pandemic. We have therefore already initiated the collection of questionnaires and serum samples and are continuing to include participants up to the time of submission of this proposal. The analysis of data and samples is pending due to lack of human and financial resources. So far 120 SC2-MI-, 50 SC2+MI-, 30 SC2-MI+ and 20 SC2+MI+ individuals have completed the questionnaire (study part A). Serum has been collected and archived from 80 SC2-MI-, 20 SC2+MI-, 20 SC2-MI+ and 10 SC2+MI+ individuals (study part B). We will include new individuals until the required sample size is achieved.

The following parameters will be recorded for study:

**Mental health**: diagnosis of psychiatric disorder, mental stress, symptoms of anxiety or depression, stigmatization, psychosocial stress factors (financial, social…), quality of life, resilience, stress coping, regular medication

**Physical health:** SARS-CoV-2 status, date of positive test result, time since positive testing, severity of COVID-19 course, persisting symptoms of COVID-19 infection, treatment received, immunization status, physical comorbidities, regular medication

**Individual variables:** sociodemographic variables such as gender, age, smoking, psychosocial factors such as income, housing situation or children or being a healthcare worker or stigma risk factors such as ethnicity, nationality.

Study part A: The main research question is to measure stigmatization in SC2-MI-, SC2+MI-, SC2-MI+ and 10 SC2+MI+. Study points will be 6 months apart and data from both time points will be used for group comparisons.

Primary research questions part A:

A1 Stigmatization is more pronounced in SC2+ vs SC2- and MI+ vs MI- and greatest in the SC2+MI+ group compared to all other groups. Group differences will not change over time (from baseline to follow-up).

A2 Mental stress is more pronounced in SC2+ vs SC2- and MI+ vs MI- and greatest in the SC2+MI+ group compared to all other groups. Group differences will not change over time (from baseline to follow-up).

A3 Symptoms of anxiety and depression are more pronounced in SC2+ vs SC2- and MI+ vs MI- and greatest in the SC2+MI+ group compared to all other groups. Group differences will not change over time (from baseline to follow-up).

Secondary research questions part A:

A5 Quality of life is lower in SC2+ compared to the SC2- and lower in MI+ compared to MI- and lowest in SC2+MI+ compared to all other groups. Group differences will not change over time (from baseline to follow-up).

A6 Resilience is lower in SC2+ vs SC2- and MI+ vs MI- and lowest in SC2+MI+ compared to all other groups. Group differences will not change over time (from baseline to follow-up).

Fig 1 shows an example of the most important proposed interactions of different factors recorded in the present study, with a focus on direct influence on the immunometabolic signature. Only the most relevant pathways of action studied are indicated for reasons of clarity, while we acknowledge that the other indicated factors also play a role. The graphical depiction demonstrates that anxiety, depression, mental stress, stigmatization as well as COVID-19 and persistence of COVID-19 symptoms are assumed to be most important. The size of the circles indicates the presumed importance of the factor. Mental health factors in red, physical health factors in blue, individual factors in green. Factors belonging to several categories are indicated by an overlay of the respective colors. Adapted and elaborated from a model by Haroon et al. 2012.

Study part B: The main research aim is to perform an immunometabolic signature including cytokines, neurotransmitter precursor amino acids and further metabolomics in SC2-MI-, SC2+MI-, SC2-MI+, SC2+MI. A hypothesis-driven approach using mixed linear modeling will be performed despite the fact that this involves oversimplification of the complex psychoimmunological mechanisms (see statistics section 2.6. for details). The hypotheses are based on our previous work on immunometabolic parameters in individuals with mental and physical disease (Hüfner et al. 2015a, Hüfner et al. 2019, Hüfner et al. 2020a).

Primary research questions part B:

B1 Stigmatization is associated with changes in the immunometabolic signature over all diagnostic groups.

B2 Inflammatory markers such as CRP, neopterin, IL-1beta, IL-6, IL-2R, IL-10, TNF-alpha are higher in SC2+ than SC2- and higher in MI+ than MI- and highest in the dual diagnosis group SC2+MI+. Group differences persist over time (from baseline to follow-up).

B3 Neurotransmitter precursor amino acid ratios (PHE/TYR and KYN/TRP) are higher in SC2+ than SC2- and higher in MI+ than MI- and highest in the dual diagnosis group SC2+MI+. Group differences persist over time (from baseline to follow-up).

B4 Acetylcarnitines are lower in the in SC2+ than SC2- and lower in MI+ than MI- and be lowest in the dual diagnosis group SC2+MI+. Group differences persist over time (from baseline to follow-up).

B5 Lysophosphatidylcholines, phosphatidylcholines sphingolipids are lower in SC2+ than SC2- and lower in MI+ than MI- and lowest in the dual diagnosis group SC2+MI-. Group differences persist over time (from baseline to follow-up).

B6 Individuals with persistent symptoms following COVID-19 show more pronounced responses in the immunometabolic signature than those with complete resolution of symptoms

Secondary research questions part B:

B7 Antibody titers against SARS-CoV-2.

In a second analysis we will take into account the complexity of the psychoimmunological approach. A path analysis using structural equation modelling will be performed following the identification of the most relevant immunometabolic parameters using a machine learning approach (see statistic section 2.6. for details and Kothari and Belsky 2021). This approach gives more credit to the complex interaction of mental and physical health as well as the influence of individual factors.

## 1.3. Innovation

Only limited data are available in the medical literature on the stigmatization during the COVID-19 pandemic. So data on stigmatization due to COVID-19 need to be collected, since the COVID-19 pandemic is at high risk for inducing stigmatization, especially due to the measures of “social distancing” (Chopra and Arora 2020). Not only are these data important to deal with the current crisis but also possible future, similar outbreaks can be managed more sustainably. The investigation of the psychoimmunological mechanisms linking stigmatization, mental stress and mental or physical disorders is an aspect that will be important beyond the current COVID-19 pandemic. It will help link psychometric and biological data thereby providing important input also for the basic science community. A healthy society caring for mental health is less vulnerable for poverty and unbalanced socioeconomic development An additional innovative aspect is brought to this study by comparing stigmatization due to mental and physical disease. These data are not only important to advance the scientific understanding of basic concepts of health and disease but are essential for the Austrian health care system and the Austrian society as a whole. If we succeed in recognizing the type, extent, and psychoimmunological consequences of stigmatization and mental stress will it be possible to use targeted measures to reduce them and thereby counteract physical and mental disease and improve the quality of life of those affected. Thus, data generated by this study will essentially support the further development of the national health care system to become more sustainable and better prepared for the post-COVID time and further crisis management. For this reason, the Medical Directors of Tirol Kliniken GmbH, Bezirkskrankenhaus Kufstein and Bezirkskrankenhaus Zams have opted to support and promote this study.

## 1.4. International research up to date

### 1.4.1. Stigmatization due to COVID-19

“Coronavirus stigma must stop — now” is the essence of an editorial of Nature magazine in April 2020. The issue of stigma associated with COVID-19 has gained much attention across the media and even this very recent editorial in the prestigious Nature magazine has taken up this topic and the associated possible consequences. “For years, it was common for viral diseases to be associated with the landscapes, places or regions where the first outbreaks occurred — as in Middle East Respiratory Syndrome (MERS), or Zika virus, named after a forest in Uganda. But in 2015, the WHO introduced guidelines to stop this practice and thereby reduce stigma and negative impacts such as fear or anger directed towards those regions or their people (...). As infectious-disease epidemiologist Adam Kucharski reminds us in his timely book *The Rules of Contagion*, history tells us that pandemics lead to communities being stigmatized, which is why we all need to exercise more care. If in doubt, seek advice, and always fall back on the consensus of the evidence.” (Editors 2020).

However, rigorous scientific studies on stigmatization during the COVID-19 pandemic are still very scarce and no studies are yet available linking stigmatization and mental stress with a biological, psychoimmunologcial approach. Recent commentaries and editorials report anecdotal evidence (Bagcchi. 2020) or deduct data from other infectious disorders (Logie 2020). Few scientific studies are available which mostly included specific groups such as health care workers (Uvais et al. 2020) or only very small samples (e.g. 5 interviews in this study Guo et al. 2020). Rigorous scientific studies are of great importance, especially since conspiracy theories, rejection and discrimination outside any scientific grounds can fuel stigmatization (Sotgiu and Dobler 2020). Therefore scientific data on the topic of SARS-CoV-2 and stigmatization are urgently needed in order to be able to “fall back on the consensus of the evidence” as pointed out in the editorial.

### 1.4.2. Experiences from the SARS epidemic

The SARS epidemics led to a pronounced stigmatization of individuals living in Amory Gardens, the first officially recognized site of community outbreak of SARS in Hong Kong, which was hit very hard by the epidemic (Lee et al., 2005). In a general population sample of Taiwanese residents, 9.7% reported that they, their family, or their friends had experienced SARS-related discrimination (Peng et al., 2010). Stigmatization resulted not only from one’s identity as a survivor or the relationship to a survivor but for example also to the health status prior to the outbreak (Siu et al., 2007).

### 1.4.3. Stigmatization due to mental health disorder

Patients with mental health disorders not only suffer from the symptoms and disabilities resulting from the illness, but also from the consequences regarding stereotypes and prejudice which result from misconceptions about mental illness. Both lead to reduced quality of life, social exclusion, and discrimination (Corrigan & Watson, 2002). The theoretical framework of stigma describes three intersecting levels: structural, public, and self-stigma (Hawke et al., 2013): **Structural stigma** refers to the policies and practices of institutions in positions of power that systematically restrict the rights and opportunities for people living with mental disorder. An example is the preferred dislocation of money for treatment and research on other health disorders than psychiatric illnesses (Link & Phelan, 2001). **Public stigma** refers to the attitude of the general population, including the attitude of trained professional groups (Mirabi et al., 1985), towards people with mental illness. Lastly, **self-stigma** refers to the internalization of societal attitudes and discriminatory practices (Crocker & Quinn, 2000). Self-stigma is defined as a subjective state “characterized by negative feelings (about self), maladaptive behaviour, identity transformation, or stereotype endorsement resulting from an individual's experiences, perceptions, or anticipation of negative social reactions on the basis of their mental illness” (Livingston & Boyd, 2010). Stigma resistance, which is related to individual resilience, in turn, has been suggested to be a key requirement for recovery (Firmin et al., 2016).

### 1.4.4. Stigmatization and mental stress

Stigmatisation has been identified as a major source of stress in very recent studies of individuals with COVID-19 disease (Guo et al 2020). A correlation between mental stress and the scores of a stigmatization scale were found in hemodialysis staff (Uvais et al. 2020a). Stigma can be a major stressor for people with schizophrenia and other mental illnesses, leading to emotional stress reactions (Corrigan, 2005). This association has led to the coining of the term “stigma stress” in the medical literature. Stigma is appraised as a stressor if perceived stigma-related harm exceeds an individual’s perceived coping resources. Increased stigma stress is associated with lower general stress resilience as well as with higher levels of perceived stigma (Schibalski et al. 2017).

### 1.4.5. The concept of resilience

Masten (2011) defined “resilience” as “the capacity of a dynamic system to withstand or recover from significant challenges that threaten its stability, viability, or development” and Schumacher and coworkers (2005) spoke of the phenomena that some individuals, despite marked negative circumstances and risk factors remain healthy or easily recover from adverse events, while others under comparable conditions seem to be particularly vulnerable to disorders and illness. However, adverse events do not necessarily lead to the development or retention of psychiatric symptoms. As such, the term resilience describes a coping style which is flexible and appropriate to the challenges of a given situation (Bender & Lösel, 1998).

### 1.4.6. Psychoimmunological aspects of mental stress and psychiatric disorders

“Mental stress is not a vague concept somehow related to the decline in the influence of traditional codes of behaviour, dissatisfaction with the world, or the rising cost of living, but (…) clearly a definable biological and medical phenomenon the mechanisms of which can be objectively identified” (Seyle 1973). The term “stress” has often been used to describe a black box hiding the mechanisms promoting mental health problems (Marchand and Durand 2011) but actually there are some exact biological mechanisms underlying mental stress and its association with mental and physical disease. However, not all mechanisms have been fully understood and investigated to date. The hypothalamic-pituitary adrenocortical axis and the sympathetic adrenomedullary system are generally considered to be the two key players in the stress response (Koolhaas et al. 2011), which can also affect the immune system (Nance and Sanders 2007). The availability of neurotransmitter precursor amino acids, which are associated with the levels of neurotransmitters in the brain, can be influenced either via stress-induced immune changes or by the direct action of stress hormones on synthesizing enzymes (Hüfner et al. 2019; Hüfner al. 2020a).

This immunomodulatory action of mental stress is one of the basic concepts of psychoneuroimmunology. This means that mental stress-induced alterations in an individual´s immunological signature lead to physical and/or mental disease, thereby resulting in overall reduced quality of life. However, this is a bi-directional relationship since also the immunological changes associated with a physical disorder can in return lead to mental symptoms such as depression, a possibility that has also been discussed in the context of SARS-CoV-2, however, only on a more theoretical basis so far (Brietzke et al. 2020). Social rejection as experienced with stigmatization is thought to specifically relate to psychoneuroimmunological changes observed with depressive symptoms (Slavich and Irwin 2014).

Overall, psychoimmunological mechanisms are complex, involving factors of mental and physical health as well as individual factors such as age, gender or smoking status. Our own research in the field of psychoimmunology has taught us that; while many factors (e.g. severity of somatic symptoms, medication, gender….) can all influence the psychoimmunological signature, physical inflammatory disease and mental illness have more significant impact on it compared to all other factors (Hüfner et al. 2015a, 2019, 2020a). Recently the first publications have started to emerge for individuals following COVID-19 infection linking peripheral lymphocyte, neutrophil, and platelet counts and severity of depressive symptoms (Mazza et al. 2021) and IL-1beta levels with depression and anxiety scores (Hu et al 2020).

### 1.4.7. Own research in the field

In this project, our Department can combine three of its main research expertises to very positively promote and advance the project: scientists at the Division of Psychiatry II (Research group leader: Katharina Hüfner, Head: Barbara Sperner-Unterweger) focus on the role of mental stress and resilience in psychiatric and psychosomatic disease and are experienced in psychoimmunology (Hüfner et al., 2015a, b, c, 2019, 2020a, b Koudouovoh-Tripp et al., 2020, Ower et al., 2019). Drs. Hüfner and Sperner-Unterweger have experience with online clinical data collection (Egeter et al., 2017). Scientists at the Division of Psychiatry I (Head: Alex Hofer) have experience in working with stigma, resilience and quality of life in patients with serious mental illnesses (e.g. Wartelsteiner et al., 2016; Hofer et al., 2016, 2017, 2019; Post et al., 2018; Mizuno et al., 2016; Mizuno et al., 2018). Scientists at the Division of psychology (Director: Bernhard Holzner) have worked extensively on quality of life research and electronic data collection (e.g. Holzner et al. 2012, Snyder et al. 2019). Together with our colleagues from the Metabolomics Core Facility (Herbert Oberacher e.g. Humpel et al. 2020; Marksteiner et al. 2019; Doppler et al. 2017, Oberacher et al. 2017) and the Institutes of Biological Chemistry (Dietmar Fuchs who established the kynurenine to tryptophan ratio (Kyn/Trp) as the tryptophan breakdown index e.g. Lanser et al. 2020, De Picker et al. 2019, Arnhard et al. 2018) and Medical Biochemistry (Johanna Gostner e.g. Gostner et al. 2020, Geisler et al. 2015) at the Medical University Innsbruck (MUI) we will be able to investigate the immunometabolic signatures with up-to-date methods, since especially research on tryptophan metabolism and neopterin formation has a long and successful history at the MUI. Aspects of physical health, especially infectious/immunological aspects will be covered via a collaboration with the Department of Infectiology and Immunology (Katharina Kurz (Schroecksnadel)), where there is extensive experience in investigating consequences of an activated immune system following infectious disorders and where the care of acute and chronic COVID-19 patients takes place (Lanser et al. 2020, Schroecksnadel et al. 2008, Knoll et al. 2020).

# 2. Study design

This section in brief: This is a longitudinal cohort study with assessments at baseline and 6 months follow-up. Recruitment of patients has been ascertained. Mixed models including covariates will be used for hypothesis testing. Additionally for the psychoimmunological approach a more explorative analysis method using machine learning and path analysis will be applied. Gender aspects will be taken into account.

## 2.1. Type of Study

This is a prospective longitudinal observational cohort study with data collection at two time points about 6 months apart.

## 2.2. Planned interventions

Since this is an observational study no direct interventions are planned. However, individuals will receive feedback to the online questionnaires (study part A). In case of conspicuous scores, information for self- help or professional help will be provided. From study part B, participants will receive feedback concerning their standard laboratory values as well as SARS-CoV-2 antibody titer. The flowchart of the study overview STIGMA-STRESS-IMMUN can be found in Appendix 2.

## 2.3. Sample description and data collection

Participants will be recruited using the following inclusion criteria:

- Individuals screened positive (at least 3 months post COVID-19 infection, date of testing ist available) or negative for SARS-CoV-2 via PCR analysis at Tirol Kliniken GmbH, BKH Kufstein, or Krankenhaus St. Vinzenz, Zams. These individuals will be contacted through cooperation with the Medical Directors of the respective study sites.

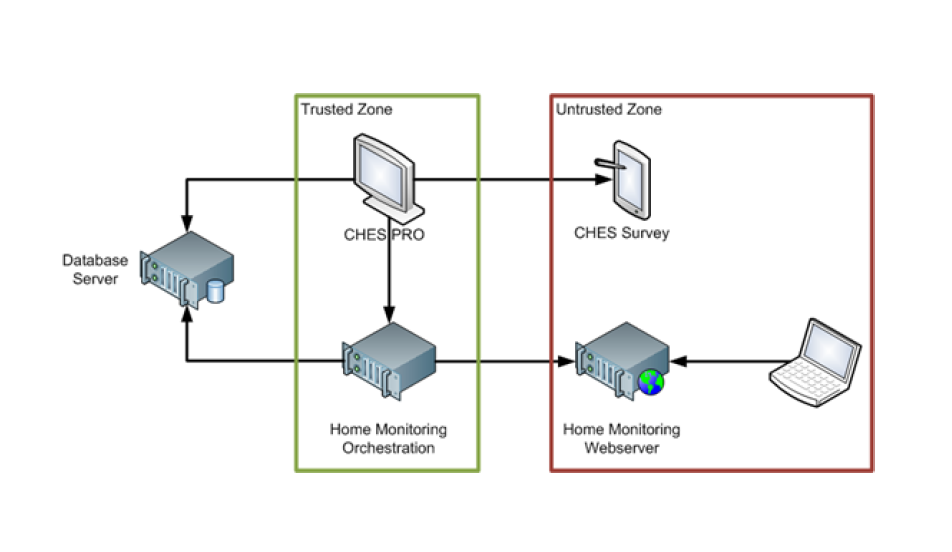
- Patients with psychiatric disorders who are regularly treated at the outpatient units of the Department of Psychiatry, Psychotherapy and Psychosomatics of the MUI, or at the psychiatric divisions of the Hospitals in Kufstein and Zams

- Resident in Tyrol

- Age: 18-70 years

- Working knowledge of German language

For the blood analysis (study part B), pregnant women will be excluded as well as individuals with active malignancies, transplantation, prior surgery in the past 3 months, or acute infection (at least 3 months post COVID-19 infection) or immunization (at least 3 months post immunization).

Fig. 2: CHES Architecture

Electronic data capture will be available by means of the Computer-based Health Evaluation System (CHES). CHES is a web-based software program that enables electronic data assessment in routine practice and clinical trials (Holzner et al. 2012). It allows multicenter study monitoring providing electronic case report forms and web-based assessment of clinical and patient-reported data. CHES has already been implemented in other studies at the MUI. Confidentiality is one of the main design goals of CHES. The security concept builds upon existing security infrastructure provided by the operating system forming a so-called trusted zone that only authorized users may have access to, e.g., restricted by user accounts of the operating system (Figure 2). Untrusted zones on the other hand can be accessed by anyone.

## 2.4. Primary and secondary endpoints

The hypotheses and research questions concerning the study endpoints can be found in section 1.2.

Study part A: The primary endpoint is the score on the SIS questionnaire as a measure of stigmatization, scores of mental stress (PSS) and Likert scales of stress, anxiety and depression (HADS). Secondary endpoints: resilience (RS-13), quality of life (WHOQOL-Bref).

Study part B: The primary research endpoint is the immunometabolic signature which will be obtained by quantifying multiple categories of endogenous metabolites, including amino acids with a special emphasis on neurotransmitter precursor amino acids, biogenic amines, acylcarnitines, phosphatidylcholines, lysophosphatidylcholines, sphingomyelins, steroid hormones and other immunomodulatory metabolites containing a cholesterol backbone as well as inflammation related cytokines. Secondary endpoints part B: Antibody titer of SARS-CoV-2.

## 2.5. Risk assessment

Part A is a questionnaire-based study with no risk is associated. Part B is the study of psychoimmunological parameters. We will draw approx. 20 ml of venous blood. The risk of this procedure is minimal.

## 2.6. Statistics / Sample size

*Sample size and power considerations*

We plan to include 100 SC2-MI+, 100 SC2+MI-, and 200 SC2-MI-, as well as 50 SC2+MI+ individuals. These numbers seem realistic and achievable considering a figure of approx. almost 50 000 positive tests conducted in Tyrol up to the date of submission, and a point prevalence of psychiatric disorders around 30% of the population.

Study part A: Power analysis was done for the group comparisons in the primary hypotheses of part A. Under standard assumptions regarding type-one error, power and within-subject correlation for repeated measures (alpha=0.05, 1-beta=0.8, r=0.5), the sample size in the four groups (50, 100, 100, 200) is sufficient to detect an effect size of between-group effects with f=0.153 by repeated-measures two-way analysis of variance (ANOVA), with two time points: baseline and 6 months follow-up), see Statistical Methods. This effect sizes lies in the small (f=0.1) to medium (f=0.25) range (Cohen 1992).

For psychoimmunological analyses (study part B), we assume that about half of the participants will agree to a blood analysis resulting in 225 blood samples at two time points. The corresponding effect sizes that can be detected in a repeated measures ANOVA (with two time points: baseline and 6 months follow-up) is f=0.217 This is a medium effect size according to Cohen’s classification. Statistically significant results have been obtained in comparable studies of psychoimmunological mechanisms in individuals with somatic and mental comorbidites (Hüfner et al. 2015a, 2019)

*Statistical Methods*

All statistical testing will be performed at a 0.05 level of significance.

*Preliminary testing:* Prior to the analysis, all psychological scales and immunological parameters will be checked for deviations from normality by investigating their skewness. Variables with skewness values >1 or <1 will be subjected to an appropriate “normalizing” transformation (e.g., square root or log) before the subsequent parametric analysis.

Analyses for the hypotheses in part A will be done with linear mixed models, that use the respective outcome variable of the hypothesis as dependent variable. The models will comprise the binary group variables MI+/- and SC2+/- as between-group effects and a time point variable (baseline and 6 months follow-up) as within-group effect. To analyze all components of the hypotheses in a joint model, the models will also include the two-way interactions MI+/- by SC2+/-, time point by MI+/-, and time point by SC2+/-. Next to the main effects, the model will include a random baseline and use a first-order autocorrelation covariance matrix. In addition, pairwise post-hoc comparisons of subgroups will be performed, provided that the interaction term had attained statistical significance. If the groups show significant associations with possible confounders (such as specific individual variables) or variables of mental or physical health, appropriate adjustments will be done. A comparable approach will be employed for analyzing the immunolometabolic parameters.

In an exploratory analysis, associations between stigmatization and mental stress as well as depressive or anxiety symptoms will be investigated by correlation analyses (Pearson correlation). Furthermore, we will investigate the model shown in Figure 1 using structural equation modelling techniques. To assess model-data-fit of the model in Figure 1 we will rely on the comparative fit index (CFI) and the Tucker-Lewis Index (TLI) (Hu and Bentler 1999). For both, values ≥ 0.95 indicate a good fit, and values >0.90 an acceptable fit. We will also use the Root Mean Square Error of Approximation (RMSEA) as an indicator of model fit, with values < 0.05 indicating a good fit, and between 0.05 and 0.08 an acceptable fit (Schermelleh-Engel et al. 2003). Prior to including immunometabolic parameters, machine learning methods (such as elastic net regression) will be employed for selecting the most relevant parameters for inclusion in the model.

## 2.7. Methods used for bias reduction

Prior to the main analyses, the sample will be checked for comparability of groups regarding individual and clinical variables. If significant differences between the groups should occur, the potential confounders will be added to the subsequent analyses within the linear mixed models. By this, the potential bias introduced by the imbalance of the distribution of covariates is largely reduced.

## 2.8. Assessment battery

**Sociodemographic data**

**Risk factors for stigmatization**: Status as a health care worker, BMI, ethnicity, nationality, living in a ski resort or larger city, having been stigmatized due to race, sex or occupation previously

**COVID-related data**: date of positive test, severity of symptoms, treatment received, oxygen, persistence of symptoms

**Data on mental and physical health:** prior diagnosis of mental or physical disorder, treatment received, current medication

**Experienced stigmatization:** *Social Impact Scale* (*SIS;* Fife & Wright, 2000; Eichhorn et al., 2015)

The 24-item SIS~~,~~ examines four domains (factors) of perceived stigma: social rejection, financial insecurity, internalized shame, and social isolation. Responses are rated on a 4-point Likert-scale. An adapted version of the SIS will be used in individuals with SARS-CoV-2 negative test results.

**Resilience:** *Resilience Scale* (Wagnild & Young, 1993)

The 13-item short form of the Resilience Scale (RS-13) validated by Leppert et al. (2008) conceptualizes resilience as a protective personality factor that is associated with a healthy development and psychosocial stress-resistance, using a 7-point Likert scale*.*

**Stress**

*Perceived Stress Scale* (*PSS*; Cohen et al., 1983)

This 10-item instrument measures the degree to which situations in one's life during the preceding month have been stressful on a 5-point scale ranging from 0 (never) to 4 (very often).

*Likert Scale to measure stress*

We will use a Likert Scale format to measure subjective stress in general, due to COVID-19 disease, due to mental health disease, and due to an individually indicated factor.

**Suicidal ideation:** *Beck Depression Inventory* (*BDI;* Beck et al., 1961)

Suicidal ideation will be assessed using the respective item (I) of the BDI.

**Quality of Life:** *WHOQOL-BREF (The WHOQOL Group, 1998)*

The WHOQOL-BREF consists of 26 questions scored in the following domains: global quality of life, physical health, psychological health, social relationships, and environment. Each question is rated on a 5-point scale, domain scores are transformed to lie between 0 and 100.

**Psychosocial Stress Scale:** *Patient Health Questionnaire* (*PHQ*; Löwe et al., 2002) - subscale on psychosocial stress factors

The PHQ is a standardized questionnaire which contains 78 items, the subscale on psychosocial stress factors and functioning contains 10 items to be rated on a 4 point Likert scale.

**Anxiety and depression symptoms:** *Hospital Anxiety and Depression Scale* (*HADS*; Zigmond & Snaith, 1983)

The HADS measures anxiety and depressive symptoms. The HADS comprises 14 items: a 7-item subscale on anxiety and a 7-item subscale on depression. The total possible score range for each subscale is 0 to 21.

**Severity of psychiatric symptoms** (patients with psychiatric disorders only): *The Clinical Global Impression* (*CGI*; Guy, 1976) rating scales

The CGI-S (severity) planned to be used in the current study is a 7-point scale that rates the overall severity of the illness.

**Evaluation concerning past and present medical history** (For study part B)

**Stress Symptoms and Coping** (For study part B): *Stress-Coping-Inventar (SCI;* Satow, 2012*)*

The SCI subscales assessing somatic and mental stress symptoms as well as the subscale assessing coping mechanisms will be administered. Ratings are done on a 4 point Likert scale.

## 2.9. Availability of patients, recruiting

Almost 50 000 individuals have been tested positive for SARS-CoV-2 in the Tyrol so far. We will continue to contact a large number of them through the formal cooperation with the head offices (“Ärztliche Direktion”), which has already been established. Patients tested positive for SARS-CoV-2 will not be included in the acute phase of the infection. 7000 patients with mental disorders are treated at the outpatient unit of the Department of Psychiatry, Psychotherapy and Psychosomatics of the MUI each year, slightly smaller numbers in the Hospitals of Kufstein and Zams.

## 2.10. Psychoimmunological analyses (study part B)

### 2.10.1. Blood draw

A total of 20 ml of venous blood will be drawn between 7:30 and 8:00 a.m. using standard clinical procedure (baseline and 6 months). Standard laboratory values will be determined at the hospital central laboratory. For the further immunological analyses samples will be shock frozen and stored at -80 until analysis.

### 2.10.2. Metabolomics

Metabolic phenotyping will be accomplished by the Core Facility Metabolomics of the MUI (Prof. Herbert Oberacher). Endogenous compounds will be analysed with a targeted quantitative and quality controlled metabolomics approach using the AbsoluteIDQ® p180 Kit (BIOCRATES Life Science AG, Innsbruck, Austria). This validated assay allows for the comprehensive identification and quantification of 186 endogenous metabolites, including amino acids, biogenic amines, acylcarnitines, phosphatidylcholines, lysophosphatidylcholines, and sphingomyelins. The targeted analysis is performed by applying flow injection analysis-tandem mass spectrometry (FIA-MS/MS), as well as liquid-chromatography-tandem mass spectrometry (LC-MS/MS) with multiple reaction monitoring (MRM) in positive electrospray ionisation mode. Quantification is achieved with internal standards.

### 2.10.3. Cytokines

Cytokines (IL-1beta, IL-6, IL-2R, IL-10, TNF-alpha) and hsCRP as well as neopterin analysis will be performed using ELISA technology in the laboratory of Assoc. Prof. Dr. J. Gostner and Prof. D. Fuchs.

### 2.10.4. Neurotransmitter precursor amino acids and related biogenic amines

Neurotransmitter precursor amino acids and downstream metabolites (kynurenic and quinolinic acid) will be analyzed in the laboratory of Assoc. Prof. Dr. Johanna Gostner and Prof. Dietmar Fuchs using HPLC and LC-MS/MS technology. Phenylalanine and tyrosine are included in the metabolomics screen described above.

### 2.10.5. Cortisol and other steroid hormones and immunomodulatory metabolites

Cortisol, cortison, steroid hormones and other immunomodulatory metabolites containing a cholesterol backbone (e.g. bile acids) will be analysed by the Core Facility Metabolomics of the MUI (Prof. Herbert Oberacher) with LC-MS/MS.

### 2.10.6. SARS-CoV-2 Antibodies

SARS-CoV-2 antibodies will be tested in the Neuroimmunology Laboratory of MUI (Prof. Florian Deisenhammer).

## 2.11. Gender Aspects

Individuals of all genders (female, male, diverse) can participate in the study. We aim to achieve a relatively homogeneous distribution between female and male participants. However, due to epidemiological aspects SARS-CoV-2 positive individuals might more often be male and individuals with certain mental health disorders will probably have a female preponderance. We will analyze the data taking gender aspects into account.

## 2.12. Cooperations

**Medical Director, Bezirkskrankenhaus Kufstein:** Assoc. Prof. Dr. Carl Miller

**Medical Director Krankenhaus St. Vinzenz, Zams:** Assoc. Prof. Dr. Eduard Wöll

**Bezirkskrankenhaus Kufstein, Division of Psychiatry:** Assoc. Prof. Dr. C. Miller (Head of Division)

**Krankenhaus St. Vinzenz, Zams, Division of Psychiatry and Psychotherapeutic Medicine:** Assoc. Prof. Dr. Martin Kurz (Head of Division)

## 2.13. Work Packages and Timeline

We calculate a total of 24 months for the whole project.

**WP 1: Study setup and refinement**

This has already been done as preparatory work, adaptation of the procedure for each study site is pending.

**WP 2: COVID-19 tested individuals (1 year)**

We will continue including individuals screened positively or negatively for SARS-CoV-2 at the three study sites over a 6 month period. The follow-ups will take place 6 months later.

**WP 3: Individuals with mental health disorder (1 year)**

Individuals treated at the outpatient units of the three study site s will be included over a 6 months period. They can complete the questionnaires via tablet while at the outpatient unit or take the access code home. A follow-up will take place 6 months later.

**WP 4 Immunometabolic profiling**

Analysis of standard laboratory parameters will be performed immediately after the blood draw. For all other analyses samples will be stored at -80 °C and then analyzed in batches in the respective laboratories or core facility.

**WP 5: Data management**

Data management will take place during the whole phase of data collection. This includes among other tasks the setup of a data bank, data entry and cleaning, as well as the generation of backups.

**WP 6: Data analysis, dissemination and publication**

Data analysis will be performed after completion of the study. The results will be disseminated to the local policy makers and hospital staff to provide insight into the treatment of individuals post COVID-19 disease as well as individuals with mental health disorders. The investigators have also extensive knowledge on presenting scientific data to a broad public via print or other media to make the results available for the Austrian population, not only researchers. Additionally, the results will be published scientifically and presentation on national and international conferences will take place.

**WP 7 Career development**

Career development of applicant Katharina Hüfner and of PhD student NN (aim to complete PhD thesis) and application for follow-up projects.

# 3. Ethical and judicial principles

This section in brief: The study complies with the standard ethical and judicial principles.

The study protocol corresponds to the directives of the Declaration of Helsinki (amended in Edinburgh in 2000 and in Washington in 2008) as well as the guidelines of good laboratory practice. Ethics approval has been obtained.

## 3.1 Information and informed consent

To participate in the study, participants must read the informed consent and electronically (part A) or in person (part B) confirm her/his consent.

## 3.2. Conflict of interest

The objective of this study remains solely for the purposes of medical research and does not anticipate any economic profit. Bernhard Holzner is owner of the intellectual property rights of the software CHES.

## 3.3. Data Handling

All participant-related data will be stored in a codified manner. Participants will receive a personalized access code to participate in the study. The codification list will be stored by the two PIs in a safe place. Blood samples will also be stored, processed and analyzed in a codified manner.

# 4. Human Resources

This section in brief: All collaborating partners of this project have extensive and internationally acclaimed experience in performing the role and tasks assigned in this project. Collaboration between the project partners has been established during prior joint projects.

## 4.1. Involved researchers

**Katharina Hüfner**

Katharina Hüfner is a board certified neurologist as well as a specialist in Psychiatry, and Psychotherapeutic Medicine. From 2009-2013 she served on the board of directors at the German Center for Dizziness and Balance founded by the Excellence initiative of the BMBF (Ministry for education and research, Germany). She was leader of a BMBF founded young scientist group from 2009 -2013 and is leader of the research group “Psychosomatic Medicine” at the Division of Psychiatry II since 2018. She serves as the deputy head of the clinical PhD program at the MUI since 2019 and as an Associate Editor of the journal BMC Psychiatry since 2020. She is a member of the European Initiative “Dizzynet” to promote clinical and scientific advancement in the field of vertigo and dizziness.

Role in the project: Coordination of the project activities, mentoring the PhD student and monitoring the progress of the project together with Co-PI Alex Hofer. She will be available for the project partners performing the immunometabolic analyses as well as the cooperating study sites for discussion as well as for patients in case of questions or concerns.

**Alex Hofer**

Alex Hofer is Professor and Head of the Division of Psychiatry I at the Department of Psychiatry, Psychotherapy and Psychosomatics of the MUI. He is Head of the Psychosis Research Group. In addition, he is a certified psychotherapist with a specialty in systemic therapy. His primary research interests relate to schizophrenia and affective disorders, cognition, resilience, quality of life, and psychopharmacology.

Role in the project: Coordination of the project activities within the Division of Psychiatry I. In addition, he will monitor the progress of the project together with PI Katharina Hüfner.

**Barbara Sperner-Unterweger**

Barbara Sperner-Unterweger is Professor and Chair of the Department of Psychiatry, Psychotherapy and Psychosomatics and Head of the Division of Psychiatry II at the MUI. She is a certified psychotherapist and Head of the clinical PhD program neuroscience. She is leader of the section of consiliar/liaison psychiatry and psychosomatic medicine of the Austrian Society of Psychiatry and Psychotherapy. Psychoimmunological and stress-related projects represent a main research interest.

Role in the project: mentoring Katharina Hüfner and help with the interpretation and dissemination of data.

**Bernhard Holzner**

Bernhard Holzner is the Director of the Division of Clinical Psychology at the Department of Psychiatry, Psychotherapy and Psychosomatics of the MUI and has more than 20 years of experience as a researcher in the field of quality of life and patient-reported outcomes (PROs) in medicine. In this research context, Bernhard Holzner has published on the development of PRO and utility questionnaires as well as on clinical trials with PRO endpoints.

Role in the project: responsible for electronic data collection in cooperation with CHES as well as data management.

**Georg Kemmler**

Georg Kemmler is a biostatistician and Associate Professor at the Division of Psychiatry I. His main areas of research comprise statistical methods in psychiatric research and methodological aspects. He has coauthored more than two hundred scientific papers.

Role in the project: supervision of data management and execution of statistical analyses, if necessary in conjunction with the Institute of Bioinformatics (director: Zlatko Trajanoski)

**N.N. 1 (PhD student)**

He/She will be responsible to recruit patients for study participation and answer questions of possible participants. In case a psychiatric assessment is necessary, he/she will refer to the respective psychiatrists of the study sites. N.N. 1 will also contact participants for inclusion into study part B and perform the study assessments in part B. N.N. 1 will be involved in sample and data management and statistical analyses and will subsequently complete his/her PhD’s degree on the topic of stigma stress.

**N.N. 2 (assistant)**

He/She will be responsible for administrative and organizational activities. He/She will also support the study sites in Zams and Kufstein with organizational issues to assure high participation rates throughout.

**Herbert Oberacher**

Herbert Oberacher is an analytical chemist and the Head of an independent research group at the Institute of Legal Medicine and the scientific Head of Institute of the Core Facility of the MUI. His research focuses on the development of new and advanced techniques for the analysis of bioorganic molecules with special emphasis on small molecules and nucleic acids and on the application of analytical chemistry in medical, biological, pharmaceutical, and environmental research.

Role in the project: responsible for parts of the described immunological profiling (metabolomics, steroid profiling), interpretation of results.

**Johanna Gostner**

Johanna Gostner is biologist and toxicologist and works in the field of biochemical and immunotoxicology, with a particular interest in immunobiochemical signalling processes that are affected by external factors such as diet and pollution. In 2015, she build up an independent junior research group, supported by the prestigious Hertha-Finberg fellowship at the Institute of Biochemistry at the MUI.

Role in the project: responsible for parts of the immunological profiling (ELISA measurements, tryptophan metabolism).

**Dietmar Fuchs**

Dietmar Fuchs is an analytical chemist, whose scientific work throughout the past 30 years was focusing on the interaction between the immune system and biochemical pathways. The metabolism of neopterin and other pteridines represented a central aspect as well as the tryptophan-kynurenine and serotonin connection. Necessary analytical methods have been established which allowed to investigate their clinical relevance.

Role in the project: Supervision and advice on scientific strategies and the interpretation of results.

**Florian Deisenhammer**

Florian Deisenhammer is a neurologist at MUI. He is the head of the Neuroimmunology Laboratory which is a “quality Austria” certified laboratory.

Role in the project: SARS-CoV-2 antibody testing.

**Katharina Kurz**

Katharina Kurz is a specialist in Internal Medicine at the Department of Infectiology, Immunology, Pneumatology and Rheumatology. Her research focusses on the relationship between immune-mediated alterations of amino acid metabolism and mental health in patients with infectious diseases.

Role in the project: care of patients following COVID-19 infection and assistance and supervision in all questions regarding infectiologic or immunologic parameters in SC2+ individuals.

## 4.2. Career development

The present project helps to develop the scientific career of Katharina Hüfner by obtaining support from the more senior collaborators, while strengthening existing scientific cooperations further. The PhD student will have the opportunity to complete her/his PhD thesis and work in a highly qualified multidisciplinary team. After finishing this project, both will have the opportunity to generate follow-up projects.

# 5. Abbreviations

ANOVA- analysis of variance

BDI - Beck depression inventory

BKH- Bezirkskrankenhaus

CHES - Computer-based Health Evaluation System

COVID-19 - Coronavirus disease

CRP – C- reactive protein

ELISA- enzyme linked immunosorbent assay

FIA-MS/MS - flow injection analysis-tandem mass spectrometry

GCI - The Clinical Global Impression

HADS - hospital anxiety and depression scale

HPLC - high performance liquid chromatography

IL-interleukin

KA-kynuric acid

KYN – kynurenine

LC-MS/MS - liquid-chromatography-tandem mass spectrometry

MUI- Medical University Innsbruck

MRM - multiple reaction monitoring

PHE - phenylalanine

PHQ - Patient Health Questionnaire

RRO-patient reported outcome

PSS – Perceived Stress scale

QA - quinolonic acid

RS-13 – Resiliencescale 13

SARS-CoV-2 - severe adult respiratory distress syndrome corona virus-2

SC2-MI- - healthy individuals

SC2+MI- individuals following COVID-19 (not in acute disease phase) without mental illness

SC2-MI- - individuals living with a mental illness who have not been tested positive for SARS-CoV-2 SC2+MI+ - individuals with dual diagnosis

SCI - Stress Coping Inventar

SIS - social impact scale

TNF – tumor necrosis factor

TRP – tryptophan

TYR - tyrosine

WHOQOL - WHO Quality of Life assessment

# Appendix 1

## Appendix 1. a. Details on the research institution

The Department for Psychiatry, Psychotherapy and Psychosomatics at the Medical University Innsbruck is composed of the Divisions of Psychiatry I and II as well as the Divisions of Medical Psychology and Child and Adolescent Psychiatry. The participating Divisions of Psychiatry I and II have eight inpatient units with more than 100 beds, a day clinic as well as a general outpatient unit. Both Divisions (I and II) also offer specialized outpatient units such as for individuals with psychosomatic disorders, anxiety disorders, affective disorders, or schizophrenia. Approximately 7000 outpatients are treated each year. The participating centers in Kufstein and Zams are both regional hospitals with specialized outpatient units for Psychiatry. Immuno (biochemical) measurements will be performed at the Institutes of Medical Biochemistry and Biological Chemistry at the Medical University Innsbruck while SARS-CoV-2 Antibody titers will be performed at the Neuroimmunology Laboratory; necessary methods and research infrastructure is available.

The mission of the Core Facility Metabolomics is to serve as an enabling resource for research and development programs at the Medical University of Innsbruck. We aim to provide expertise and state-of-the-art technologies for the qualitative and quantitative analysis of small bioorganic molecules. Common targets are drugs, pharmaceuticals, endogenous compounds, and metabolites thereof included in all kinds of biological samples (e.g. biofluids, cells, tissues). More information on the Core Facility Metabolomics is provided at <https://biomassspec.gmi.tirol/corefacility/>.

Project participants who are not financed by funds applied for in the framework of this project

Innsbruck:

Assoc. Prof. Dr. Katharina Hüfner

Prof. Dr. Alex Hofer

Prof. Dr. Bernhard Holzner

Prof. Dr. Barbara Sperner-Unterweger

Assoc. Prof. Dr. Georg Kemmler, PhD (statistician)

Assoc. Prof. Dr. Herbert Oberacher

Prof. Dr. Dietmar Fuchs

Assoc. Prof. Dr. Johanna Gostner

Prof. Dr. Florian Deisenhammer

Assoc. Prof. Dr. Katharina Kurz

Kufstein:

Assoc. Prof. Dr. Carl Miller

Dr. Johann Margreiter

Zams:

Assoc. Prof. Dr. Martin Kurz

Dr. Arnold Schiechtl

## Appendix 1. b. Information on requested funding

Personnel costs

PhD student (N.N. 1): 24 months, 30 hours/week = € 79 564

He/She will be responsible to recruit patients for study participation and answer questions of possible participants. In case a psychiatric assessment is necessary he/she will refer to the local medical specialists. N.N. 1 will perform the blood draws and interviews during study part B. He/She will be involved in data management and statistical analyses and will subsequently complete his/her PhD’s degree on the topic stigma-induced mental stress and underlying psychoimmunological mechanisms.

Assistant (N.N. 2): 24 months, 10 hours/week= € 19 140

He/She will be responsible for administrative and organizational activities such as the preparation of questionnaires, generation and mailing of the access codes, preparation of blood draws, communication with participants concerning organizational issues. He/She will also support the study sites in Zams and Kufstein with organizational issues to assure high participation rates throughout.

MTF (Mag. Simon Geisler) 6 months (5%) + 12 months (30%) = 15 330

He will be responsible for preparing the blood samples for analyses, for performing the ELISA readings and assisting with the HPLC measurements.

SUM PERSONEL COSTS: € 114 030

Travel-costs

**Reimbursement for N.N. 1 or N.N. 2.** To travel to the study sites in Zams and Kufstein to interact with colleagues or collect and process blood samples 2000 Euro

**Travel costs for study participants**:Individuals participating in part B of the study (immunological signature) will be compensated for travel expenses to and from the study site. Estimated costs: 450 visits (225 individuals), average 20 Euro per visit: 9000 Euro

SUM TRAVEL COSTS: 11 000 Euro

Materials

**Cytokines Analyses ELISA**: 5 ELISA plates per parameter (225 samples x 2 timepoints) with duplicate measurements of 6 parameters 37 590.00 Euro + VAT=45 108 Euro

**Consumables laboratory:** 5000 Euro this includes regular consumables for blood processing, transport between study sites, labelling and storage as well as for ELISA measurements and HPLC analysis of tryptophan metabolites.

**SARS-CoV-2 Antibody titer**: The Neuroimmunology Laboratory will need 6720 Euro. This includes 6 ELISA kits at approx. 800 Euro/piece which have been quality controlled at the Neuroimmunology Laboratory as well as 3 Elisa kits from a different company at a little lower price (approx. 600 Euro each) to verify positive cases.

**Metabolomics:** Biocrates kits for targeted metabolome analyses will be purchased at Euro 16 734.00 for 225 samples including controls x2 = 33 468 Euro. Analyses will be performed by the Core Facility metabolomics (Prof. Herbert Oberacher).

SUM MATERIALS: 90 368 Euro

Other

**CHES:** This professional online data collection tool allowing for collection of sensitive data such as psychiatric diagnoses will be customized for the present study. 15 800 Euro

**Metabolomics:** Analyses of Biocrates kits will be performed by the Core Facility Metabolomics (Prof. Herbert Oberacher). The core facility will charge 10 Euro processing charge per sample resulting in 4500 Euro

**Cortisol and related immunactive steroids:** The Core Facility metabolomics will charge 50 Euro per sample for the analysis of cortisol and related metabolites via LC-MS/MS resulting in 22 500 Euro

**Insurance for participants:** Individuals participating in part B of the study (immunological signature) will be insured via the Tirol Klink at Zürich Versicherung for 20 Euro per participant: 4000 Euro total

SUM OTHER: 45 000 Euro

INTERIM TOTAL: 262 198.00

General costs (5% of the interim total): € 13 109.90

TOTAL COSTS: € 275 307.90

# Appendix 2: Summary of the clinical study

1) Title of Clinical Trial: Comparing stigmatization and perceived mental stress in COVID-19 or mental health disorders – a psychoimmunological approach (STIGMA-STRESS-IMMUN)

2) Figure study overview (most important abbreviations: healthy individuals (SC2-MI-), individuals following COVID-19 without mental illness (SC2+MI-), individuals living with a mental illness who have not been tested positive for SARS-CoV-2 (SC2-MI+) as well as individuals with dual diagnosis (SC2+MI+).

**Individuals tested for COVID-19 outside the Dep of Psychiatry**

**Patients with mental disorder from the Dep. of Psychiatry**

**SC2-MI+ (100)**

**SC2+MI+ (50)**

**SC2-MI- (200)**

**SC2+MI- (100)**

**Included groups**

**CGI score-severity scale**

**Study Part B**

**Study Part A**

Online questionnaires, codified data collection, personalized access codes

**methods**

Stress related immunological profiling in 225 samples, individuals will be invited following questionnaire completion

On day of blood collection: detailed medical history including COVID-19 disease,(updated values of PSS scale, HADS scale, Stress Coping Inventory (SCI), PHQ psychosocial stress)

CRP, neopterin, blood count

Metabolome analyses including amino acids (including neurotransmitter precusor amino acids), acylcarnitines, phosphatidylcholines, lysophosphatidylcholines, sphingomyelins)

Cortisol and metabolites

Cytokines: IL-1beta, IL-6, IL-2R, IL-10, TNF-alpha

SARS-CoV-2 antibody titer

Individual variables: sociodemographics, psychosocial factors, stigma risk factors

Physical health: SARS-CoV-2 status, date of test result, severity of COVID-19 course, persisting symptoms of COVID-19 infection, treatment received, immunization status, physical comorbidities, regular medication

Mental health: diagnosis of psychiatric disorder, regular medication

Sigma: Social Impact Scale (SIS)

Mental Stress: Cohen Perceived Stress Scale (PSS), Likert Scales Stress

Quality of life: WHOQOL BREF

Psychosocial stress: PHQ subscale

Suicidal ideation: BDI 1 item

Depression/Anxiety: Hospital Anx./Dep. Scale (HADS)

Resilience: Resiliencescale-13 (RS-13)

**questionnaires**

**parameters**

Individuals will receive results routine laboratory tests as well as SARS-CoV-2 antibody titer

Participants will receive feedback on HADS scores, resilience and stress levels. Information with self-help suggestions and professional support numbers/addresses will be provided

**benefit for patients**

**timescale**

Baseline + 6 month follow up

3) Applicant: Assoc. Prof. Dr. Katharina Hüfner

Department of Psychiatry, Psychotherapy and Psychosomatics

Division of Psychiatry II

Medical University Innsbruck

Anichstr. 35

6020 Innsbruck

4) Clinical Trial Type: Longitudinal observational study with two part; study part A: online questionnaire based part, part B: immunometabolic signature.

5) Objectives: The study is designed to investigate mental and physical health across 4 groups: healthy individuals (SC2-MI-), individuals following COVID-19 (not in acute phase of disease) without mental illness (SC2+MI-), individuals living with a mental illness who have not been tested positive for SARS-CoV-2 (SC2-MI+) as well as individuals with dual diagnosis (SC2+MI+). We hypothesize that the stigmatization, mental stress as well as anxiety and depression will differ between the groups and show most pronounced values in the dual diagnosis group. Additionally to the main research question, we will assess resilience and quality of life. In a psychoimmunological approach, basic biological mechanisms underlying the complex bi-directional relationship between mental and physical disease will be explored taking parameters of mental (e.g. severity of depressive symptoms) and physical health (e.g. persistence of COVID-19 symptoms) as well as confounding factors (e.g. gender) into account. We will assess participants immunolometabolic signature including a metabolome approach and proinflammatory cytokines. SARS-CoV-2 antibody titers will be determined.

These data are not only important to advance scientific understanding but are essential for the Austrian health care system and society as a whole. If we succeed in recognizing the type and extent of stigmatization in the context of the COVID-19 pandemic it will be possible to use targeted measures to reduce it and thus counteract mental stress and improve the quality of life of those affected. Leading experts in the field are already calling for programs to improve mental health in the COVID and “post COVID” world (World Economic Forum). Sound and large scale scientific data are needed to back those claims and to correctly allocate financial resources. The current study aims to contribute here.

The biological data will ground the psychometric data on a psychoimmunological foundation and can elucidate underlying mechanisms which will be relevant far beyond the current pandemic.

6) Intervention: No direct intervention is planned. However, we will provide a feedback document on individual psychometric scores with information for self-help and professional support. In addition, laboratory values and SARS-CoV-2 antibody results will be provided.

7) Key inclusion and exclusion criteria: Individuals screened positive or negative for SARS-CoV-2 at Tirol Kliniken GmbH, Bezirkskrankenhaus Kufstein, or Krankenhaus St. Vinzenz, Zams (at least 3 months post acute disease phase), patients with mental health disorders treated at the psychiatric units of these clinics, resident in Tyrol, age: 18-70 years, working knowledge of German language. There are no exclusion criteria for the psychometric part of the study (part A). Pregnant women as well as individuals with active malignancies, following transplantation, prior surgery or immunization in the past 3 months, or acute infection will be excluded from the immunometabolic signature (part B).

8) Study part A: The primary endpoint is the score on the SIS (Social Impact Scale) questionnaire as a measure of stigmatization, scores of mental stress (PSS) and measures of anxiety and depression (HADS), secondary endpoints are resilience (RS-13) and quality of life (WHOQOL BREF).

Study part B: The primary research endpoint is the immunometabolic signature, which will be obtained by quantifying multiple categories of endogenous metabolites including amino acids with a special emphasis on neurotransmitter precursor amino acids, biogenic amines, acylcarnitines, phosphatidylcholines, lysophosphatidylcholines, sphingomyelins, steroid hormones, and other immunomodulatory metabolites containing a cholesterol backbone as well as inflammation related cytokines.Secondary endpoints are ntibody titer against SARS-CoV-2.

9) Sample Size, Statistical Analyses, Power Calculation: We plan to include 100 SC2-MI+, 100 SC2+MI-, and 200 SC2-MI-, as well as 50 SC2+MI+ individuals. These numbers seem achievable given approx. 50 000 positive tests conducted in Tyrol at the time of submission, and a point prevalence of psychiatric disorders around 30% of the population. Under standard assumptions regarding type-one error, power and within-subject correlation for repeated measures (alpha=0.05, 1-beta=0.8, r=0.5), the sample size in the four groups (study part A) is sufficient to detect an effect size of between-group effects with f=0.153 by repeated-measures two-way analysis of variance (ANOVA), with two time points: baseline and 6 months follow-up. For psychoimmunological analyses (study part B), we assume that about half of the participants will agree to a blood analysis. This will allow to detect effects with f=0.217. Such an effect size is expected from previous studies of psychoimmunological mechanisms (Hüfner et al. 2015a, 2019).

Analyses for the hypotheses in part A will be done with linear mixed models that use the respective outcome variable of the hypothesis as dependent variable. The models will comprise the binary group variables MI+/- and SC2+/- as between-group effects and a time point variable (baseline and 6 months follow-up) as within-group effect. To analyze all components of the hypotheses in a joint model, the models will also include the two-way interactions of the between- and within-group effects If the groups show significant associations with possible confounders (such as specific individual variables) or variables of mental or physical health, appropriate adjustments will be done. A comparable approach will be employed for analyzing the immunolometabolic parameters. Furthermore, we will analyze psychoimmunological mechanisms by using structural equation modelling techniques. We will rely on the comparative fit index, the Tucker-Lewis Index and the Root Mean Square Error of Approximation to determine model-data fit. Prior to including immunometabolic parameters, machine learning methods (such as elastic net regression) will be employed for selecting the most relevant parameters.

10) Trial Duration: The time between the two study time-points is 6 months. As preparatory work we have started recruitment and archived serum samples for analysis as soon as funding is available. The duration of the entire trial including immunometabolic analyses will be 2 years.

11) Participating Centers: Tirol Kliniken GmbH, Medical Director and Department of Psychiatry, Psychotherapy and Psychosomatics, Divisions of Psychiatry I and II, Medical University Innsbruck.; Bezirkskrankenhaus Kufstein, Medical Director and Division of Psychiatry; Krankenhaus St. Vinzenz, Zams, Medical Director and Division of Psychiatry and Psychotherapy.

# Appendix 3: References

Arnhard K, Pitterl F, Sperner-Unterweger B, Fuchs D, Koal T, Oberacher H. A Validated Liquid Chromatography-High Resolution-Tandem Mass Spectrometry Method for the Simultaneous Quantitation of Tryptophan, Kynurenine, Kynurenic Acid and Quinolinic Acid in Human Plasma. Electrophoresis 2018; 39:1171-1180.

Bagcchi S. Stigma during the COVID-19 pandemic. Lancet Infect Dis. 2020;20:782.

Bender D, Lösel F. Protektive Faktoren der psychisch gesunden Entwicklung junger Menschen: Ein Beitrag zur Kontroverse um saluto- und pathogenetische Ansätze. In Margraf J, Siegrist J, Neumer S (eds.). Gesundheits- oder Krankheitstheorie? Saluto- vs. pathogenetische Ansätze im Gesundheitswesen. Berlin: Springer, 1998; pp.119-145.

Beck, AT., Ward, C. H., Mendelson, M., Mock, J., Erbaugh, J. An inventory for measuring depression. Archives of General Psychiatry 196; 4:561-571.

Bonanno GA, Westphal M, Mancini AD. Resilience to loss and potential trauma. Annu Rev Clin Psychol 2011; 7:511-535.

Brietzke E, Magee T, Freire RCR, Gomes FA, Milev R. Three insights on psychoneuroimmunology of mood disorders to be taken from the COVID-19 pandemic. Brain Behav Immun Health. 2020;5:100076.

Chopra KK, Arora VK. Covid-19 and social stigma: Role of scientific community. Indian J Tuberc. 2020;67:284-285. doi:10.1016/j.ijtb.2020.07.012

Cohen J. A power primer. Psychol Bull 1992; 112:155-159.

Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983; 24:385-396.

Corrigan PW. On the stigma of mental illness: Practical strategies for research and social change. American Psychological Association; Washington: 2005.

Corrigan PW, Watson AC. Understanding the impact of stigma on people with mental illness. World Psychiatry 2002; 1:16–20.

Crocker J, Quinn DM. Social stigma and the self: meanings, situations, and self-esteem. In: Heatherton TF, Kleck RE, Hebl MR, Hull JG (Eds.). The Social Psychology of Stigma, Guilford Press, New York, NY, US; 2000:pp 153-183.

De Picker L, Fransen E, Coppens V, Timmers M, de Boer P, Oberacher H, Fuchs D, Verkerk R, Sabbe B, Morrens, M. Immune and Neuroendocrine Trait and State Markers in Psychotic Illness: Decreased Kynurenines Marking Psychotic Exacerbations. Frontiers in Immunology - Section Inflammation, 2019 accepted.

Doppler C, Arnhard K, Dumfarth J, Heinz K, Messner B, Stern C, Koal T, Klavins K, Danzl K, Pitterl F, Grimm M, Oberacher H, Bernhard D. Metabolomic Profiling of Ascending Thoracic Aortic Aneurysms and Dissections - Implications for Pathophysiology and Biomarker Search. PLOS One, 12 (2017), e0176727.

Editors. Stop the coronavirus stigma now. Nature 2020; 580:165.

Egeter J, Hüfner K, Sztankay M, Holzner B, Sperner-Unterweger B. Implementation of an electronic routine outcome monitoring at an inpatient unit for psychosomatic medicine. J Psychosom Res 2018; 105:64-71.

Eichhorn S, Mehnert A, Stephan M. German version of the Social Impact Scale – pilot testing of an instrument for measuring experienced stigmatization in a sample of cancer patients. Psychother Psych Med 2015; 65:183-190.

Fife BL, Wright ER. The dimensionality of stigma: a comparison of its impact on the self of persons with HIV/AIDS and cancer. J Health Soc Behav 2000; 41:50-67.

Firmin RL, Luther L, Lysaker PH, Minor KS, Salyers MP. Stigma resistance is positively associated with psychiatric and psychosocial outcomes: a meta-analysis. Schizophr Res 2016; 175:118-128.

Friborg O, Hjemdal O, Rosenvinge JH, Martinussen M, Aslaksen PM, Flaten MA. Resilience as a moderator of pain and stress. J Pychosom Res 2006; 61:213–219.

Geisler, S., Mayersbach, P., Becker, K., Schennach H., Fuchs, D., Gostner, J. M., Serum tryptophan, kynurenine, phenylalanine, tyrosine and neopterin concentrations in 100 healthy blood donors Pteridines 2015; 26(1). 31-36. https://doi.org/10.1515/pterid-2014-0015 |

Gooding PA, Hurst A, Johnson J, Tarrier N. Psychological resilience in young and older adults. Int J Geriatr Psychiatry 2012; 27:262-270.

Gostner JM, Geisler S, Stonig M, Mair L, Sperner-Unterweger B, Fuchs D. [Tryptophan Metabolism and Related Pathways in Psychoneuroimmunology: The Impact of Nutrition and Lifestyle.](https://www.ncbi.nlm.nih.gov/pubmed/30808841) Neuropsychobiology. 2020; 79:89-99.

Guo Q, Zheng Y, Shi J, et al. Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: A mixed-method study. Brain Behav Immun. 2020;88:17-27. doi:10.1016/j.bbi.2020.05.038

Guy W. Clinical Global Impressions. ECDEU assessment manual for psychopharmacology, revised (DHEW Publ No ADM 76-338). National Institute of Mental Health, Rockville, MD 1976:pp 218-222.

Haroon, E., Raison, C. L., & Miller, A. H. (2012). Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. Neuropsychopharmacology 37, 137–162. https://doi.org/10.1038/npp.2011.205

Hawke LD, Parikh SV, Michalak EE. Stigma and bipolar disorder: a review of the literature. J Affect Disord 2013; 150:181-191.

Hofer A, Mizuno Y, Frajo-Apor B, Kemmler G, Suzuki T, Pardeller S, Welte A, Sondermann C, Mimura M, Wartelsteiner F, Fleischhacker WW, Uchida, H. Resilience, internalized stigma, self-esteem, and hopelessness among people with schizophrenia: cultural comparison in Austria and Japan. Schizophr Res 2016; 171:86-91.

Hofer A, Mizuno Y, Wartelsteiner F, Wolfgang Fleischhacker W, Frajo-Apor B, Kemmler G, Mimura M, Pardeller S, Sondermann C, Suzuki T, Welte A, Uchida H. Quality of life in schizophrenia and bipolar disorder: The impact of symptomatic remission and resilience. Eur Psychiatry 2017;46:42-47.

Hofer A, Post F, Pardeller S, Frajo-Apor B, Hoertnagl CM, Kemmler G, Fleischhacker WW. Self-stigma versus stigma resistance in schizophrenia: Associations with resilience, premorbid adjustment, and clinical symptoms. Psychiatry Res 2019; 271:396-401.

Holzner B, Giesinger JM, Pinggera J, Zugal S, Schöpf F, Oberguggenberger AS, Gamper EM, Zabernigg A, Weber B, Rumpold G. [The Computer-based Health Evaluation Software (CHES): a software for electronic patient-reported outcome monitoring.](https://www.ncbi.nlm.nih.gov/pubmed/23140270) BMC Med Inform Decis Mak 2012;12:126.

Hu LT. and Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Struct Equ Modeling 1999; 6 (1): 1-55.

Hu Y, Chen Y, Zheng Y, You C, Tan J, Hu L, Zhang Z, Ding L. Factors related to mental health of inpatients with COVID-19 in Wuhan, China. Brain Behav Immun. 2020 Oct;89:587-593

Huang et al., “6-month consequences of COVID-19 in patients discharged from hospital: a cohort study.” Lancet [2021 doi.org/10.1016/S0140-6736(20)32656-8](https://doi.org/10.1016/S0140-6736(20)32656-8)).

Hüfner K, Oberguggenberger A, Kohl C, Geisler S, Gamper E, Meraner V, Egeter J, Hubalek M, Beer B, Fuchs D, Sperner-Unterweger B. Levels in neurotransmitter precursor amino acids correlate with mental health in patients with breast cancer. Psychoneuroendocrinology 2015 a; 60:28-38.

Hüfner K, Kandler C, Koudouovoh-Tripp P, Egeter J, Hochstrasser T, Stemer B, Malik P, Giesinger J, Humpel C, Sperner-Unterweger B. Bioprofiling of platelets in medicated patients with depression. J Affect Disord. 2015b; 172:81-8.

Hüfner K, Koudouovoh-Tripp P, Kandler C, Hochstrasser T, Malik P, Giesinger J, Semenitz B, Humpel C, Sperner-Unterweger B. Differential changes in platelet reactivity induced by acute physical compared to persistent mental stress. Physiol Behav. 2015c; 151:284-91.

Hüfner K, Fuchs D, Blauth M, Sperner-Unterweger B. How acute and chronic physical disease may influence mental health – An Analysis of neurotransmitter precursor amino acid levels. Psychoneuroendocrinology 2019; 106:95-101.

Hüfner K, Galffy M, Egeter J, Giesinger JM, Arnhard K, Oberacher H, Gostner JM, Fuchs D, Sperner-Unterweger B. Acute and Chronic Mental Stress Both Influence Levels of Neurotransmitter Precursor Amino Acids and Derived Biogenic Amines. Brain Sci. 2020a 26;10:322. doi: 10.3390/brainsci10060322.

Hüfner K, Ower C, Kemmler G, Vill T, Martini C, Schmitt A, Sperner-Unterweger B. Viewing an alpine environment positively affects emotional analytics in patients with stress-related psychiatric disorders. BMC Psychiatry 2020b , Doi: 10.21203/rs.3.rs-15834/v1

Humpel, H., Foidl, B. M., Oberacher, H., Marksteiner, J. Platelet and Plasma Phosphatidylcholines as Biomarkers to Diagnose Cerebral Amyloid Angiopathy. Frontiers in Neurology - Section Multiple Sclerosis and Neuroimmunology, 2020 accepted.

Koolhaas, J.M., Bartolomucci, A., Buwalda, B., de Boer, S.F., Flugge, G., Korte, S.M. and others. Stress revisited: a critical evaluation of the stress concept. Neurosci Biobehav Rev 2011; 35:1291-1301.

Kothari M, Belsky DW. Unite to predict. Elife. 2021 Feb 12;10:e66223. doi: 10.7554/eLife.66223. PMID: 33576740; PMCID: PMC7880680.

Koudouovoh-Tripp P, Hüfner K, Egeter J, Kandler C, Giesinger JM, Sopper S, Humpel C, Sperner-Unterweger B. Stress enhances proinflammatory platelet activity: the impact of acute and chronic mental stress. 2020; accepted.

Knoll M, Hofer S, Schroll A, Fuchs D, Geisler S, Gostner JM, Weiss G, Bellmann-Weiler R, Kurz K. Fatigue, depression and quality of life in patients with post-infectious fatigue – a prospective, double-blind, placebo-controlled study. Pteridines 2020; 31: 118.

Lanser L, Kink P, Egger EM, Willenbacher W, Fuchs D, Weiss G, Kurz K. Inflammation-induced tryptophan breakdown is related with anemia, fatigue, and depression in cancer. Front Immunol 11:249, 2020).

Lee S, Chan LYY, Chau AMY, Kwok KPS, Kleinman A. The experience of SARS-related stigma at Amoy Gardens. Social Science & Medicine 2005; 61:2038-2046.

Leonard, B.E., Myint, A. The psychoneuroimmunology of depression. Hum Psychopharmacol 2009; 24:165-175.

Leppert K, Koch B, Brähler E, Strauß B. Die Resilienzskala (RS) - Überprüfung der Langform RS-25 und einer Kurzform RS-13. Klinische Diagnostik und Evaluation 2008;2:226-243.

Link BG, Phelan JC. Conceptualizing stigma. Annu Rev Sociol 2001; 27:363-385.

Link BG, Struening EL, Neese-Todd S, Asmussen S, Phelan JC. Sigma as a Barrier to Recovery: The Consequences of Stigma for the Self-Esteem of People With Mental Illnesses. Psychiatric Services 2001; 52:1621-1626.

Link BG, Phelan JC. Stigma and its public health implications. Lancet 2006; 367:528-529.

Logie CH. Lessons learned from HIV can inform our approach to COVID-19 stigma. J Int AIDS Soc. 2020;23:e25504.

Löwe B, Spitzer RL, Zipfel S, Herzog W. Gesundheitsfragebogen für Patienten (PHQ D). Komplettversion und Kurzform. 2. Auflage. Karlsruhe: Pfizer; 2002.

Marchand, A., Durand, P. Psychological distress, depression, and burnout: similar contribution of the job demand-control and job demand-control-support models? J Occup Environ Med 2011; 53:185-189+

Marksteiner, J., Oberacher, H., Humpel, C. Acyl-alkyl-phosphatidlycholines Are Decreased in Saliva of Alzheimer´s Disease as Identified by Targeted Metabolomics. Journal of Alzheimer's Disease 291; 68:583-589.

Masten AS. Resilience in children threatened by extreme adversity: frameworks for research, practice, and translational synergy. Dev Psychopathol 2011; 23:493-506.

Masten AS, Obradović J. Competence and resilience in development. Ann N Y Acad Sci 2006; 1094:13-27.

Masten AS, O'Dougherty Wright M. Resilience over the lifespan: developmental perspectives on resistance, recover and transformation. In Reich JW (ed.): Handbook of adult resilience, New York NY, Guilford Press; 2010:pp213-237.

Mazza M G, Palladini M., De Lorenzo R., Magnaghi C., Poletti S., Furlan R., Ciceri F., Rovere- Querini P., Benedetti F. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up, Brain, Behavior, and Immunity (2021), doi: <https://doi.org/10.1016/j.bbi.2021.02.021>

Mirabi M, Weinman ML, Magnetti SM, Keppler KN. Professional attitudes toward the chronic mentally ill. Hosp Community Psychiatry 1985; 36:404-405.

Mizuno Y, Hofer A, Suzuki T, Frajo-Apor B, Wartelsteiner F, Kemmler G, Saruta J, Tsukinoki K, Mimura M, Fleischhacker WW, Uchida H. Clinical and biological correlates of resilience in patients with schizophrenia and bipolar disorder: A cross-sectional study. Schizophr Res 2016; 175:148-153.

Mizuno Y, Hofer A, Frajo-Apor B, Wartelsteiner F, Kemmler G, Pardeller S, Suzuki T, Mimura M, Fleischhacker WW, Uchida H. Religiosity and psychological resilience in patients with schizophrenia and bipolar disorder: an international cross-sectional study. Acta Psychiatr Scand 2018; 137:316-327.

Nance DM, Sanders VM. Autonomic innervation and regulation of the immune system (1987-2007). 1. Brain Behav Immun. 2007; 6:736-45. Epub 2007 Apr 27.

Oberacher, H., Arnhard, K., Linhart, C., Diwo, A., Marksteiner, J., Humpel, C.\* Targeted Metabolomic Analysis of Soluble Lysates from Platelets of Patients with Mild Cognitive Impairment and Alzheimer's Disease Compared to Healthy Controls: Is PC aeC40:4 a Promising Diagnostic Tool? Journal of Alzheimer's Disease 2017; 57:493-504.

Ower C, Kemmler G, Vill T, Martini C, Schmitt A, Sperner-Unterweger B, Hüfner K. The effect of physical activity in an alpine environment on quality of life is mediated by resilience in patients with psychosomatic disorders and healthy controls. Eur Arch Psychiatry Clin Neurosci. 2019; 269:543-553.

Peng EY, Lee MB, Tsai ST, Yang CC, Morisky DE, Tsai LT, Weng YL, Lyu SY. Population-based post-crisis psychological distress: an example from the SARS outbreak in Taiwan. J Formos Med Assoc. 2010; 109:524-532.

Post F, Pardeller S, Frajo-Apor B, Kemmler G, Sondermann C, Hausmann A, Fleischhacker WW, Mizuno Y, Uchida H, Hofer A. Quality of life in stabilized outpatients with bipolar I disorder: Associations with resilience, internalized stigma, and residual symptoms. J Affect Disord 2018; 238:399-404.

Satow, L. Stress- und Coping-Inventar (SCI): Test- und Skalendokumentation. Online im Internet, URL: [http://www.drsatow.de](http://www.drsatow.de/) Copyright © 2012 Dr. L. Satow

Schibalski JV, Müller M, Ajdacic-Gross V, Vetter S, Rodgers S, Oexle N, Corrigan PW, Rössler W, Rüsch N. Stigma-related stress, shame and avoidant coping reactions among members of the general population with elevated symptom levels. 1. Compr Psychiatry. 2017;74:224-230. doi: 10.1016/j.comppsych.2017.02.001. Epub 2017 Feb 4.

Schermelleh-Engel K, Moosbrugger H and Müller H. Evaluating the fit of structural equation models: Tests of significance and descriptive goodness-of-fit measures. MPR-Online 2003; 8 (2): 23-74.

Schroecksnadel K, Sarcletti M, Winkler C, Mumelter B, Weiss G, Fuchs D, Kemmler G, Zangerle R. Quality of life and immune activation in patients with HIV-infection. Brain Behav Immun. 2008;22:881-9.

Schumacher J, Leppert K, Gunzelmann T, Strauß B, Brähler E. Die Resilienzskala–Ein Fragebogen zur Erfassung der psychischen Widerstandsfähigkeit als Personmerkmal. Z Klin Psychol Psychiatr Psychother 2005; 53:16-39.

Selye, H. The evolution of the stress concept. Am Sci 1973; 61:692-699.

Siu JY, Sung HC, Lee WL. Qigong practice among chronically ill patients during the SARS outbreak. J Clin Nurs 2007; 16:769-76.

Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014; 140:774-815. doi: 10.1037/a0035302. Epub 2014 Jan 13.

Snyder C, Smith K, Holzner B, Rivera YM, Bantug E, Brundage M; PRO Data Presentation Delphi Panel. Making a picture worth a thousand numbers: recommendations for graphically displaying patient-reported outcomes data. Qual Life Res. 2019; 28:345-356.

Sotgiu G, Dobler CC. Social stigma in the time of coronavirus disease 2019. Eur Respir J. 2020;56:2002461. doi:10.1183/13993003.02461-2020

The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med 1998; 28:551-558.

Uvais NA, Aziz F, Hafeeq B. COVID-19-related stigma and perceived stress among dialysis staff. J Nephrol. 2020, 17:1–2.

Wagnild GM, Young HM. Development and psychometric evaluation of the Resilience Scale. J Nursing Meas 1993; 1:165–178.

Wartelsteiner F, Mizuno Y, Frajo-Apor B, Kemmler G, Pardeller S, Sondermann C, Welte A, Fleischhacker WW, Uchida H, Hofer A. Quality of life in stabilized patients with schizophrenia is mainly associated with resilience and self-esteem. Acta Psychiatr Scand 2016; 134:360-367.

Wingo AP, Briscione M, Norrholm SD, Jovanovic T, McCullough SA, Skelton K, Bradley B. Psychological resilience is associated with more intact social functioning in veterans with post-traumatic stress disorder and depression. Psychiatry Res 2017; 249:206-211.

Wagnild GM, Young HM. Development and psychometric evaluation of the Resilience Scale. J Nursing Meas 1993; 1:165–178.

# Appendix 4 Curriculum vitae

**Assoc. Prof. Dr. Katharina Hüfner**

<https://orcid.org/0000-0002-5453-8792>

Born 16.10.1976

10/2016-10/2018 Maternity leave

**CLINICAL EDUCTION AND EXPERIENCE**

2020 Certified specialist in Psychiatry and Psychotherapeutic Medicine

Since 2013 Medical doctor, Department of Psychiatry, Psychotherapy, and Psychosomatics, Division of Psychiatry II (Psychosomatic Medicine), Innsbruck Medical University, Innsbruck, A

2012 Certified Specialist in Neurology

2009-2013 Member of the Board of directors, German Center for Vertigo and Balance Disorders IFBLMU

2004-2013 Medical doctor Department of Neurology, Ludwig-Maximilians University, Munich, GER,

2002/2003 Final year internships: Mount Sinai School of Medicine, NYC, NY; Dartmouth Medical School, Hanover, NH, USA; Hospital for Neurology and Neurosurgery at Queen Square, London, GB

2001 Clinical electives abroad: WHO-Health-Centre, Nuuk, Greenland; Ayr Hospital, Ayr, QEENSL, AUS; Rockingham and Kwinana District Hospital, Perth, WA, A

1998-2003 Ludwig-Maximilians University Medical School, Munich, GER

1996-1998 Albert-Ludwigs University Medical School, Freiburg, GER, Royal Infirmary, Aberdeen, GB

**RESEARCH ACTIVITIES AND POSITONS**

Since 2020 Associate editor BMC Psychiatry

Since 2020 Associate Professor, Medical University Innsbruck, Innsbruck, A

Since 2018 Leader of the research group “Psychosomatic Medicine”

2016-2020 Assistant Professor, Medical University Innsbruck, Innsbruck, A

Since 2013 Research in stress-related psychiatric disorders, psychoneuroimmunology and psychosomatic medicine, Department of Psychiatry, Psychotherapy and Psychosomatics (Head: Prof. Dr. B. Sperner-Unterweger), Innsbruck Medical University, Innsbruck, AUS

2010 Habilitation (venia legendi Clinical Neurology), Ludwig-Maximilians University, Munich,GER

2009-2013 Leader “Young Scientist Group”, Ludwig-Maximilians University, Munich, GER, funded by the Excellence Initiative of German Ministery for Education and Research (BMBF)

2004-2013 Research on the vestibular and ocular motor system with special focus on neuroimaging studies and molecular biology techniques, Department of Neurology, Ludwig-Maximilians University, Munich, GER

1999-2000 Research at Salk Institute for Biological Studies, LaJolla, CA, USA and CNRS, Grenoble, FR

**SCHOLARSHIPS AND EXTERNAL FUNDING (excerpt)**

2020-2023 External funding by the Austrian Climate and Energy Fond

2012-2015 External funding by Jubiläumsfond of the Austrian National Bank (principal investigator: Prof. Dr. B. Sperner-Unterweger)

2011 External funding by the “Verein für wissenschaftliche Psychiatrie”

2009-2015 External funding by the German Ministery for Education and Research (BMBF)

2007-2014 External funding by the Research and Teaching Incentive Program of the Ludwig-Maximilians University, Munich, GER

2005 External funding by the „Friedrich Baur Stiftung“

2000 Graduate scholarship from the “Deutsche Forschungs-Gemeinschaft” (German Academic Exchange Program, DAAD)

1999-2000 PhD scholarship from the “Deutsche Forschungs-Gemeinschaft” (German Research Foundation, DFG)

**TEACHING EXPERIENCE (only recent activities)**

Since 2019 Deputy Head for the clinical PhD program “Neurosciences” at Medical University Innsbruck, Innsbruck, A

since 2018 Teaching of specialized course in “Psychosomatic Medicine”, Medical University Innsbruck, Innsbruck, A

**10 RELEVANT PUBLICATIONS**

Bayer O, Bremova T, Strupp M, **Hüfner K.** A randomized double-blind, placebo-controlled, cross-over trial (Vestparoxy) of the treatment of vestibular paroxysmia with oxcarbazepine. J Neurol. 2018;265:291-298. doi: 10.1007/s00415-017-8682-x.

Egeter J, **Hüfner K**, Sztankay M, Holzner B, Sperner-Unterweger B. Implementation of an electronic routine outcome monitoring at an inpatient unit for psychosomatic medicine. J Psychosm Res. 2018;105:64-71. doi: 10.1016/j.jpsychores.2017.12.009

**Hüfner K,** Binetti C, Hamilton DA, Stephan T, Flanagin VL, Linn J, Labudda K, Markowitsch H, Glasauer S, Jahn K, Strupp M, Brandt T. Structural and functional plasticity of the hippocampal formation in professional dancers and slackliners. Hippocampus. 2011 Aug;21(8):855-65. doi: 10.1002/hipo.20801.

**Hüfner K**, Brugger H, Caramazza F, Stawinoga AE, Broadmann-Maeder M, Gatterer H, Turner R, Tomazin I, Fusar-Poli P, Sperner-Unterweger B. (2019): Development of a self-administered questionnaire to detect high altitude psychosis – The HAPSY Questionnaire. High Alt Med Biol. 2019 Dec;20(4):352-360. doi: 10.1089/ham.2019.0009

**Hüfner K**, Brugger H, Kuster E, Dunsser F, Stawinoga AE, Turner R, Tomazin I, Sperner-Unterweger B. (2018): Isolated psychosis during exposure to very high and extreme altitude - characterisation of a new medical entity. Psychol Med. 2018;48:1872-1879. doi: 10.1017/S0033291717003397.

**Hüfner K**, Fuchs D, Blauth M, Sperner-Unterweger B. How acute and chronic physical disease may influence mental health - An Analysis of neurotransmitter precursor amino acid levels. Psychoneuroendocrinology. 2019 Aug;106:95-101. doi: 10.1016/j.psyneuen.2019.03.028.

**Hüfner K**, Kandler C, Koudouovoh-Tripp P, Egeter J, Hochstrasser T, Stemer B, Malik P, Giesinger J, Humpel C, Sperner-Unterweger B. (2015): Bioprofiling of platelets in medicated patients with depression. J Affect dis. 2015;172:81-88. doi: 10.1016/j.jad.2014.09.029.

**Hüfner K**, Koudouovoh-Tripp P, Kandler C, Hochstrasser T, Malik P, Giesinger J, Semenitz B, Humpel C, Sperner-Unterweger B. Differential changes in platelet reactivity induced by acute physical compared to persistent mental stress. Physiol Behav. 2015;151:284-291. doi: 10.1016/j.physbeh.2015.07.021.

**Hüfner K**, Oberguggenberger A, Kohl C, Geisler S, Gamper E, Meraner V, Egeter J, Hubalek M, Beer B, Fuchs D, Sperner-Unterweger B. Levels in neurotransmitter precursor amino acids correlate with mental health in patients with breast cancer. Psychoneuroendocrinology 2015;60:28-38. doi: 10.1016/j.psyneuen.2015.06.001.

Ower C, Kemmler G, Vill T, Martini C, Schmitt A, Sperner-Unterweger B, **Hüfner K**. The effect of physical activity in an alpine environment on quality of life is mediated by resilience in patients with psychosomatic disorders and healthy controls. Eur Arch Psychiatry Clin Neurosci. 2018.doi: 10.1007/s00406-018-0930-2.

**OTHER RESEARCH ACHIEVEMENTS**

1. Development of an online information and intervention program ([www.psychosomatik-innsbruck.at/Covid](http://www.psychosomatik-innsbruck.at/Covid)) with accompanying scientific evaluation during the Corona crisis, featured also in the Tiroler Tageszeitung 4/2020 and Tirol TV 4/2020
2. Participation in one of the first multidisciplinary studies performed in TerraXcube (<https://terraxcube.eurac.edu/>) to investigate the effect of simulated high altitude on humans under standardized conditions. TerraXcube is a research infrastructure in Bolzano/Bozen that simulates the Earth’s most extreme climatic conditions 10/2019. This study was covered by ORF magazine “nano”
3. Several TV appearances in ORF e.g. on high altitude psychosis together with Peter Habeler 3/2018, on mental stress 5/2019, and radio appearances e.g. on Deutschlandfunk 12/2017 and 11/2020
4. Our article Hüfner et al. on isolated high altitude psychosis was featured by the TIME magazine, NEWSWEEK magazine, Spiegel, Süddeutsche Zeitung and other media across the world like The Himalayan or NZZ 12/2017
5. Important invited lectures (only examples):

Vestibular failure & hippocampal atrophy-implications for navigation. "Hallpike Symposium", Institute for Neurology and Neurosurgery, Queen Square, UCL 17.10.2008, London, GB

Low grade inflammation-induced changes in neurotransmitter precursor amino acids and their possible role as biomarkers in cancer-related depression 35th International Winter Workshop, Clinical, Chemical and Biochemical Aspects of Pteridines and Related Topics 24.2.2016, Innsbruck, A

**Curriculum vitae Prof. Alex Hofer, MD**

ORCID: [0000-0002-5834-4258](http://orcid.org/0000-0002-5834-4258)

Medical University Innsbruck

Department of Psychiatry, Psychotherapy and Psychosomatics,

Division of Psychiatry I

<https://www.i-med.ac.at/universitaet/>

***RESEARCH FOCUS:***

Prof. Hofer’s primary research interests relate to schizophrenia, affective disorders, cognition, resilience, quality of life, and psychopharmacology.

*Present Appointment at the Department* *of Psychiatry, Psychotherapy and Psychosomatics, Medical University Innsbruck, Austria:*

11/2004 – 09/2017 Head of the schizophrenia outpatient unit and the Schizophrenia Research Group

01/2007 – 09/2017 Head of the schizophrenia inpatient unit

10/2017 – 09/2019 Acting Director of the Division of Psychiatry I

10/2019 - Head of the Division of Psychiatry I

*Past Appointments and Experience at the Medical University Innsbruck, Austria:*

1994-1996 Clinical Clerkship, Department of Neurology

1996-1997 Clinical Clerkship, Department of Psychiatry and Psychotherapy

1997-2004 Residency Training, Department of Psychiatry and Psychotherapy

01-03/2001 Residency Training, Department of Magnetic Resonance Imaging

04-12/2001 Residency Training, Department of Internal Medicine

07/2003-06/2004 Residency Training, Department of Neurology

03/2006 Associate Professor of Psychiatry

*Certifications:*

Course in Neuropsychopharmacology

Course in Magnetic Resonance Imaging and Spectroscopy

Course in Psychosocial Medicine

Course in Psychosomatic Medicine

Course in Psychotherapeutic Medicine

*Education:*

Medical Faculty, Innsbruck University, Austria

Turku University Hospital, Finland

State Hospital Starnberg, Germany

State Hospital Brunico, Italy

State Hospital, San Candido, Italy

*Memberships:* Austrian Society of Psychiatry and Psychotherapy

Austrian Schizophrenia Society

Austrian Association of Biological Psychiatry

European College of Neuropsychopharmacology (ECNP)

Schizophrenia International Research Society (SIRS)

*Awards (excerpt):*

2004 12th Biennal Winter Workshop on Schizophrenia, Davos; young scientist award

2007 9. Tagung der Österreichischen Gesellschaft für Neuropsychopharmakologie und Biologische Psychiatrie [ÖGPB], Vienna; clinical psychiatry award

2010 Schizophrenia International Research Society, travel fellowship award

2015 17. Tagung der Österreichischen Gesellschaft für Neuropsychopharmakologie und Biologische Psychiatrie [ÖGPB], Vienna; schizophrenia award (senior author)

2018 Organization of Austrian female physicians, Lore Antoine-award for diploma thesis (tutor)

*Grants (excerpt):*

2001-2005 Regional cerebral activity in schizophrenia and major depression: the impact of pharmacotherapy (Österreichische Nationalbank)

2003-2005 Sibutramine in antipsychotic-induced weight gain (Medizinischer Forschungsfonds Tirol)

2004-2005 Gender differences in regional cerebral activity during the perception of emotion: a functional MRI study (FWF)

2013-2017 Emotional Intelligence in schizophrenia and bipolar I disorder: a comparison between patients, their siblings and healthy controls (FWF)

*Keynote speeches (excerpt):*

**Hofer A**: How do cognitive deficits influence treatment and outcome in schizophrenia patients?

World Psychiatric Association, International Thematic Conference, Vienna, June 19-22, 2003.

**Hofer A:** Facial affect recognition and its relationship to symptomatic, subjective and functional outcomes in outpatients with chronic schizophrenia. 10th World Congress of Biological Psychiatry, Prague, 29.05.-02.06.2011

**Hofer A:** Emotional Intelligence in patients suffering from schizophrenia and unaffected siblings. 13th World Congress of Biological Psychiatry, Copenhagen, 18.-22.06.2017

**Hofer A:** Resilience and internalized stigma. WPA XVII World Congress of Psychiatry, Berlin, 09.-12.10.2017

**Hofer A:** Negative symptoms and cognitive deficits in schizophrenia in the ENI schizophrenia pan-European study. 27th European Congress of Psychiatry, Warsaw, Poland, April 6-9, 2019

***PUBLICATIONS OF PARTICULAR RELEVANCE:***

Frajo-Apor B, Pardeller S, Kemmler G, **Hofer A**: Emotional Intelligence and resilience in mental health professionals caring for patients with serious mental illness. Psychol Health Med 2016;21:755-761.

**Hofer A**, Mizuno Y, Frajo-Apor B, Kemmler G, Suzuki T, Pardeller S, Welte A, Sondermann C, Mimura M, Wartelsteiner F, Fleischhacker WW, Uchida H: Resilience, internalized stigma, self-esteem, and hopelessness among people with schizophrenia: cultural comparison in Austria and Japan. Schizophr Res 2016;171:86-91.

Mizuno Y, **Hofer A**, Suzuki T, Frajo-Apor B, Wartelsteiner F, Kemmler G, Saruta J, Tsukinoki K, Mimura M, Fleischhacker WW, Uchida H: Clinical and biological correlates of resilience in patients with schizophrenia and bipolar disorder: a cross-sectional study. Schizophr Res 2016;175: 148-153.

Wartelsteiner F, Mizuno Y, Frajo-Apor B, Kemmler G, Pardeller S, Sondermann C, Fleischhacker WW, Welte A, Uchida H, **Hofer A**: Quality of life in stabilized schizophrenia patients is mainly associated with resilience and self-esteem. Acta Psychiatr Scand 2016;134:360-367.

**Hofer A**, Mizuno Y, Wartelsteiner F, Fleischhacker WW, Frajo-Apor B, Kemmler G, Mimura M, Pardeller S, Sondermann C, Suzuki T, Welte A, Uchida H. Quality of life in schizophrenia and bipolar disorder: the impact of symptomatic remission and resilience. Eur Psychiatry 2017;46:42-7*.*

Mizuno Y, **Hofer A**, Frajo-Apor B, Wartelsteiner F, Kemmler G, Pardeller S, Suzuki T, Mimura M, Fleischhacker WW, Uchida H: Religiosity and psychological resilience in patients with schizophrenia and bipolar disorder: an international cross-sectional study. Acta Psychiatr Scand 2017;137: 316-327.

Post F, Pardeller S, Frajo-Apor B, Kemmler G, Sondermann C, Hausmann A, Fleischhacker WW, Mizuno Y, Uchida H, **Hofer A**: Quality of Life in stabilized outpatients with bipolar I disorder: associations with resilience, internalized stigma, and residual symptoms. J Affect Disord 2018;238: 399-404.

**Hofer A**, Pardeller S, Frajo-Apor B, Hoertnagl CM, Kemmler G, Post F: Self-stigma versus stigma resistance in schizophrenia: associations with resilience, premorbid adjustment, and clinical symptoms. Psychiatry Res 2019;271:396-401*.*

Frajo-Apor B, Pardeller S, Kemmler G, Muehlbacher M, Welte A, Hoertnagl CM, **Hofer A**: The interrelationship between Emotional Intelligence and Quality of Life in schizophrenia and bipolar I disorder. Psychiatry Res 2020; *under review*.

Siedentopf CM, Yalcin-Siedentopf N, Welte A, Steiger R, Ischebeck A, Gizewski ER, **Hofer A**. Sex differences in the neural correlates of resilience. Neuroimage 2020; *under review*.

C U R R I C U L U M V I T A E

**Holzner Bernhard, Ph.D., M.Eng., Prof.**

[**ORCID 0000-0002-3389-3621**](https://orcid.org/0000-0002-3389-3621)

**EDUCATION**

University, Constructional Engineering 1986-1992, Innsbruck  
 (Graduation M.E. June 1992)

University, Psychology, 1989-1996, Innsbruck  
 (Graduation Ph.D. July 1996)  
Education in Clinical Psychology/Health Psychology May 1994 - June 1995, Vienna

Education in behavioral therapy February 1995 - October 1999, Munich

Associate Professor (Medical Psychology, October 2003, Innsbruck

Psychosomatic Medicine, Psychotherapy,

Medical Faculty, University of Innsbruck)

Professorship (Innsbruck Medical University) January 2016, Innsbruck

**PROFESSIONAL LIFE**

Department of Biological Psychiatry, since July 1993  
Medical University Innsbruck

Member of the scientific advisory board since May 1998

University Hospital of Psychiatry, Innsbruck

Research Fellowship at CORE (Evanston, Chicago, USA) 2003

Associate director of the C/L Service, University Hospital

of Biological Psychiatry, Medical University of Innsbruck 2003 - 2017

CEO of ESD (company developing the CHES Software) since January 2004

Head of the Division of Psychology, University Hospital

of Psychiatry I, Medical University of Innsbruck since January 2016

Head of the Division of C/L Service, University Hospital

of Psychiatry II, Medical University of Innsbruck since January 2017

Honorary treasurer of the EORTC Quality of Life Group November 2011 – September 2017

**Major SCIENTIFIC AWARDS and GRANTS**

Award from the Austrian Society for Psychiatry (Pfizer ZNS-scientific award 2001/2002‘).

Erwin Schrödinger Fellowship (Austrian Science Fund), 2003.

Grant from the Fund Healthy Austria, 2002.

Award from the Center of Academic Spin offs Tyrol (CAST), 2005.

Grants from the Austrian National Bank, 2006 and 2011

Grants from the Tyrolean Quality Assurance Fund, 2008, 2012.

Grants from the Austrian Science Fund, 2008, 2014.

Grants from the European Organisation for Research and Treatment of Cancer (EORTC) 2010 and 2011, 2012, 2019

**HONORS/ AFFILIATIONS (MEMBERSHIP OR LEADERSHIP POSITIONS)**

Honorary treasurer of the EORTC Quality of Life Group

Vice-chairman of the Austrian Platform of Psychooncology

Member of the ISOQOL

Member of the BÖP (Austria)

Member of the “Österreichische Gesellschaft für Psychiatrie und Psychotherapie (ÖGPP)“

Member of the “Arbeitsgemeinschaft für Verhaltensmodifikation (AVM) “

**PUBLICATIONS**

142 publications listed in PubMed, primarily in the field of health outcome research

**Description of research achievements**

* Between 2010 and 2017 Bernhard Holzner was member of the executive committee of the EORTC Quality of Life Group
* He is a well-known specialist in developing electronic tools for the assessment of PROs.
* He is a developer of the CHES System, an electronic tool for the collection, analyses and presentation of medical as well as PRO data.

**PUBLICATIONS OF PARTICULAR RELEVANCE:**

Petersen MA, Aaronson NK, Conroy T, Costantini A, Giesinger JM, Hammerlid E, Holzner B, Johnson CD, Kieffer JM, van Leeuwen M, Nolte S, Ramage JK, Tomaszewski KA, Waldmann A, Young T, Zotti P, Groenvold M; European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group. [International validation of the EORTC CAT Core: a new adaptive instrument for measuring core quality of life domains in cancer.](https://www.ncbi.nlm.nih.gov/pubmed/31955374) Qual Life Res. 2020 May;29(5):1405-1417.

Giesinger JM, Loth FLC, Aaronson NK, Arraras JI, Caocci G, Efficace F, Groenvold M, van Leeuwen M, Petersen MA, Ramage J, Tomaszewski KA, Young T, Holzner B; EORTC Quality of Life Group. [Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research.](https://www.ncbi.nlm.nih.gov/pubmed/31639445) J Clin Epidemiol. 2020 Feb;118:1-8. doi: 10.1016/j.jclinepi.2019.10.003. Epub 2019 Oct 19.

Sztankay M, Neppl L, Wintner LM, Loth FL, Willenbacher W, Weger R, Weyrer W, Steurer M, Rumpold G, Holzner B. [Complementing clinical cancer registry data with patient reported outcomes: A feasibility study on routine electronic patient-reported outcome assessment for the Austrian Myelome Registry.](https://www.ncbi.nlm.nih.gov/pubmed/31465136) Eur J Cancer Care (Engl). 2019 Nov;28(6):e13154.

Sztankay M, Aaronson NK, Arraras JI, Basso U, Bumbasirevic U, Efficace F, Giesinger JM, Johnson CD, van Leeuwen M, Oberguggenberger AS, Sosnowski R, Young T, Holzner B; European Organisation for Research and Treatment of Cancer Quality of Life Group (EORTC QLG). [International phase IV validation study of an EORTC quality of life questionnaire for testicular cancer patients: the EORTC QLQ-TC26.](https://www.ncbi.nlm.nih.gov/pubmed/30419889) BMC Cancer. 2018 Nov 12;18(1):1104.

Snyder C, Smith K, Holzner B, Rivera YM, Bantug E, Brundage M; PRO Data Presentation Delphi Panel. [Making a picture worth a thousand numbers: recommendations for graphically displaying patient-reported outcomes data.](https://www.ncbi.nlm.nih.gov/pubmed/30306533) Qual Life Res. 2019 Feb;28(2):345-356.

Sztankay M, Giesinger JM, Zabernigg A, Krempler E, Pall G, Hilbe W, Burghuber O, Hochmair M, Rumpold G, Doering S, Holzner B. [Clinical decision-making and health-related quality of life during first-line and maintenance therapy in patients with advanced non-small cell lung cancer (NSCLC): findings from a real-world setting.](https://www.ncbi.nlm.nih.gov/pubmed/28835219) BMC Cancer. 2017 Aug 23;17(1):565.

Weis J, Tomaszewski KA, Hammerlid E, Ignacio Arraras J, Conroy T, Lanceley A, Schmidt H, Wirtz M, Singer S, Pinto M, Alm El-Din M, Compter I, Holzner B, Hofmeister D, Chie WC, Czeladzki M, Harle A, Jones L, Ritter S, Flechtner HH, Bottomley A; EORTC Quality of Life Group. [International Psychometric Validation of an EORTC Quality of Life Module Measuring Cancer Related Fatigue (EORTC QLQ-FA12).](https://www.ncbi.nlm.nih.gov/pubmed/28376231) J Natl Cancer Inst. 2017 May 1;109(5).

Wintner LM, Sztankay M, Aaronson N, Bottomley A, Giesinger JM, Groenvold M, Petersen MA, van de Poll-Franse L, Velikova G, Verdonck-de Leeuw I, Holzner B; [The use of EORTC measures in daily clinical practice-A synopsis of a newly developed manual.](https://www.ncbi.nlm.nih.gov/pubmed/27721057) EORTC Quality of Life Group. Eur J Cancer. 2016 Nov;68:73-81

Wintner LM, Giesinger JM, Zabernigg A, Rumpold G, Sztankay M, Oberguggenberger AS, Gamper EM, Holzner B. [Evaluation of electronic patient-reported outcome assessment with cancer patients in the hospital and at home.](https://www.ncbi.nlm.nih.gov/pubmed/26699708) BMC Med Inform Decis Mak. 2015 Dec 23;15:110

Holzner B, Giesinger JM, Pinggera J, Zugal S, Schöpf F, Oberguggenberger AS, Gamper EM, Zabernigg A, Weber B, Rumpold G. [The Computer-based Health Evaluation Software (CHES): a software for electronic patient-reported outcome monitoring.](https://www.ncbi.nlm.nih.gov/pubmed/23140270) BMC Med Inform Decis Mak. 2012 Nov 9;12:126.

|  |  |
| --- | --- |
| Name: | Barbara SPERNER-UNTERWEGER, Univ.-Prof. Dr.med. |
| Date of birth: | 02. September 1958 |
| Pace of birth | Klagenfurt, Austria |
| Nationality | Austria |

**Curriculum vitae Barbara Sperner-Unterweger**

|  |
| --- |
| Department for Psychiatry, Psychotherapy and Psychosomatics  Divison for Psychiatry II  Anichstrasse 35, A-6020 Innsbruck  Tel.:                 +43-(0)512-504-23629  Fax:                +43-(0)512-504-25267  E-mail:            [barbara.sperner-unterweger@i-med.ac.at](mailto:barbara.sperner-unterweger@i-med.ac.at)  Homepage:     <https://psychosomatik.tirol-kliniken.at> |

ORCID-Nummer: [0000-0001-8936-676X](https://orcid.org/0000-0001-8936-676X)

|  |  |
| --- | --- |
| 1977 - 1984 | University of Innsbruck, Dr.med univ. |
| 1984 - 1989 | Residency Training, Department of Psychiatry, University of Innsbruck |
| 1990 - 1992 | Residency Training, Department of Neurology, Department of Internal Medicine, University of Innsbruck |
| 1993 | Scholarship at the Western Psychiatric Institute, Pittsburgh, Pennsylvania |
| Since 1993 | Head of Research Team Psychoimmunology/Psychooncology  Head of the Clinical Division of Consultation-Liaison-Psychiatry |
| 1998 | Habilitation (Associated Professor) in Psychiatry, Medical University Innsbruck (MUI) |
| 2011 | Professor for Consultation-Liaison-Psychiatry and Psychosomatic Medicine, MUI |
| Since 2017 | Chair of Department of Psychiatry, Psychotherapy and Psychosomatic |

153 peer-reviewd publications, total impact factor: 405, H-index: 40, i10index: 77

Main research focus: psychosomatic medicine with a special focus on “psychophysiology” exploring psychoimmunological and stress related mechanisms in patients with depression and anxiety.

10 selected publication

1. SPERNER-UNTERWEGER B, CZEIPEK I, GAGGL S, GEISLER D, SPIEL G, FLEISCHHACKER WW (1998): Treatment of severe clozapine induced neutropenia with granulocyte colony-stimulating factor (G-CSF): remission despite continuous treatment with clozapine. **British Journal of Psychiatry** 172: 82-84. DOI: [10.1192/bjp.172.1.82](https://doi.org/10.1192/bjp.172.1.82)
2. SPERNER-UNTERWEGER B, WHITWORTH A, KEMMLER J, HILBE W, THALER J, WEISS G, FLEISCHHACKER WW (1999): T-cell subsets in schizophrenia: a comparison between drug naive episode patients and chronic schizophrenic patients. **Schizophrenia Research** 38: 61-70. DOI: [10.1016/s0920-9964(98)00175-3](https://doi.org/10.1016/s0920-9964(98)00175-3)
3. SPERNER-UNTERWEGER B (2005): Immunological aetiology of major psychiatric disorders: evidence and therapeutic implications. **CNS Drugs** 65 (11): 1493-1520. DOI: [10.2165/00003495-200565110-00004](https://doi.org/10.2165/00003495-200565110-00004)
4. KOHL C, WALCH T, HUBER R, KEMMLER G, NEURAUTER G, FUCHS D, SOLDER E, SCHRÖCKSNADEL H, SPERNER-UNTERWEGER B (2005): Measurement of tryptophan, kynurenine and neopterin in women with and without postpartum blues. **J Affect Dis** 86 (2-3):135-142. DOI: [10.1016/j.jad.2004.12.013](https://doi.org/10.1016/j.jad.2004.12.013)
5. KOHL C, SPERNER-UNTEREGER B (2007): IDO and Clinical Conditions associated with depressive symptoms. **Curr Drug Metabol** 8 (3): 283-287. DOI: [10.2174/138920007780362572](https://doi.org/10.2174/138920007780362572)
6. SPERNER-UNTERWEGER B., NERAUTER G., KLIEBER M., KURZ K., MERANER V., ZEIMET A., FUCHS D. (2011): Enhanced tryptophan degradation in patients with ovarian carcinoma correlates with several serum soluble immune activation markers. **Immunobiology** 216:296-301. DOI:[10.1016/j.imbio.2010.07.010](https://doi.org/10.1016/j.imbio.2010.07.010)
7. SPERNER-UNTERWEGER B, KOHL C, FUCHS D (2014): Immune changes and neurotransmitters: possible interactions in depression. **Progr Neuropsychopharmacol Biol Psychiatry** 48:268-276. DOI:[10.1016/j.pnpbp.2012.10.006](https://doi.org/10.1016/j.pnpbp.2012.10.006)
8. HÜFNER K, KOUDOUOVOH-TRIPP P, KANDLER C, HOCHSTRASSER T, MALIK P, GIESINGER J, SEMENITZ B, HUMPEL C, SPERNER-UNTERWEGER B (2015): Differential changes in platelet reactivity induced by acute physical compared to persistent mental stress. **Physiology & Behavior,** 151:284-291. DOI:[10.1016/j.physbeh.2015.07.021](https://doi.org/10.1016/j.physbeh.2015.07.021)
9. **HÜFNER K,** Kandler Ch, Koudouovoh-Tripp P, Egeter J, Hochstrasser t, stemer b, malik p, giesinger j, humpel ch, sperner-unterweger b (2015): Bioprofiling of platelets in medicated patients with depression.**J Affective Disorder** 172:81-88. DOI: [10.1016/j.jad.2014.09.029](https://doi.org/10.1016/j.jad.2014.09.029)
10. HÜFNER K, OBERGUGGENBERGER A, KOHL C, GEISLER S, GAMPER E, MERANER V, EGETER J, HUBALEK M, BEER B, FUCHS D, SPERNER-UNTERWEGER B (2015): Levels in neurotransmitter precursor amino acids correlate with mental health in patients with breast cancer. **Psychoneuroendocrinology** 60:28-38. DOI: [10.1016/j.psyneuen.2015.06.001](https://doi.org/10.1016/j.psyneuen.2015.06.001)

Additional Research Achievements

|  |  |
| --- | --- |
| 2012 | Sperner-Unterweger B: **Can affective disorders and schizophrenia be differentiated on an immunological basis?** 3rd Schizophrenia International Research Society Conference, 14.-18.04.2012, Florenz |
| 2013 | Sperner-Unterweger B: **Neopertin and tryptophan breakdown in schizophrenia and depression.** WPA-Kongress, 27.-30.10.2013, Wien |
| 2015 | Sperner-Unterweger B, Fuchs D: **Phenylalanine/tyrosine metabolism as a bridge between the immune system and neurochemistry.** Symposium “The Immune-brain axis: from molecules to behavior”, Hasselt 12.-13.03.2015 |
| 2015 | Sperner-Unterweger B: **Inflammation-induced disturbances of neurotransmitter precursor amino acids and their possible role as biomarkers in depression**. 12th World Congress of Biological Psychiatry, Athen,16.-18.06.2015 |
| 2018 | Sperner-Unterweger B: **The association of acute and chronic somatic disease, depressive symptoms and neurotransmitter precursor monamine levels.** 14th Psychoimmunology Expert Meeting – Neuroinflammation in Psychiatry – from basic to psychopathology. Günzburg, 23.-24.03.2018 |