

Genetic Case Studies and Causality

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ABSTRACT

Recent developments in genetics have led to a variety of new methods in medicine. Over the last two decades some completely new methodological approaches have emerged and are by now established in daily research routine. This article is focussed on Mendelian randomization, a method which uses information from genetic case studies to clarify causal relations between parameters found to be associated in multi-center epidemiological randomized trials. I argue that, with Mendelian randomization, multilevel analysis has in fact entered the stage of medicine: It could be referred to as “genetic multilevel analysis” in that it establishes causal relations by means of transition from the macro to the micro level and back. Features of multilevel analysis, as it was established in economics and sociology, and went to philosophy from there, are compared with Mendelian randomization, where at the micro level individual genetically defined polymorphic sub-populations are analyzed. Max Weber, who contributed to medical methodology himself and may be regarded as one of the founding fathers of sociology, is proposed as a major inspirator for multilevel analysis.

Summary: In terms of methodology, Mendelian randomization shares several striking features with multilevel analysis. This article argues that Mendelian randomization is in fact a multilevel analysis applied to clinical medicine.

MAX WEBER AND MULTILEVEL ANALYSIS

The fact that Max Weber exerted such an enormous influence on such a great number of different disciplines makes it both tempting and dangerous to claim him as the forefather of any given method or idea. Being one of the founders of sociology he stands at the beginning of social measurement as such, he was influential in the early development of a scientific approach to sociological analysis, as well as several other areas from economics to philosophy and medicine. Most of his ideas were soon picked up by his pupils who tended to become more specialized scholars so that a certain divergence of his original lines of thought was unavoidable. In terms of methodology, Weber gave rise to what was soon to develop into „methodological individualism“ and „multilevel analysis“, two lines of thought which are closely related in sociology, their main assumption being that „purposeful action can only be exerted by one or several single persons“ (Max Weber). In his article “Meanings of methodological individualism”, published in the Journal of economic methodology in 2007¹, Geoffrey Hodgson traces the term “methodological individualism” back to 1908 when it was coined by Austrian economist Joseph Schumpeter. Schumpeter was to become one of the founders of the Austrian school of economic thought, Max Weber had been his academic teacher. Although Weber himself never used the terms of either “methodological individualism” or “multilevel analysis” himself, Hodgson states that “... in the first chapter of his ‘Economy and Society’, published after his death in 1920, he promoted a position that has since been described as methodological individualism.” From economics, the term “...was exported into other disciplines”, as Hodgson puts it, “through the Austrian trinity of Schumpeter, Hayek and von Mises: Popper’s student John W. N. Watkins advocated a version of the doctrine and stimulated a protracted controversy in the philosophical literature. In the 1960s the phrase made its first appearance in a leading sociological journal (Dore, 1961)“. According to Wolfgang Schluchter² it

was David McClelland who first promoted the position that the connection between „methodological individualism“ and „multilevel analysis“ may be illustrated with Weber’s study about „ascetic protestantism and the spirit of capitalism“ of 1905. However, the more different disciplines use a term, the more difficult it is to know what one is talking about, and Hodgson argues: „Despite its frequent appearance, there is no consensus on ... sense and usage [of ‘methodological individualism’]. Hence there is no warrant for the incantation of its two words without reference to an adequate definition.“ Therefore, this article will refer to „multilevel analysis“ only. Hartmut Esser argues, that in his pivotal essay on ascetic protestantism Weber established the crucial method of sociological explaining, and that any sound explanation in sociology has to be a multilevel analysis. James Coleman used the same early study of Weber’s to show the transition from the macro to the micro level and back, which was to become the hallmark of multilevel analysis. In the following paragraphs the main features of multilevel analysis will be discussed and the recent genetic method of Mendelian randomization will be introduced. I hope to demonstrate, that this method developed purely out of practical necessity in medical epidemiology in the 1990ies without any of the pioneers ever referring to Weber or sociology - still the method as it stands today is an application of multilevel analysis to medicine.

THE EXPLANANTIA OF MULTILEVEL ANALYSIS IN SOCIOLOGY

One could enter into lengthy discussions at this point, as to whether looking at individuals makes any sense for analysis

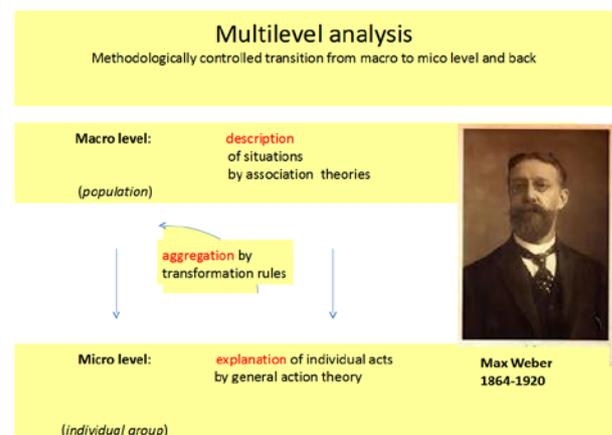


Figure1: scheme of transitions between macro and micro levels in multilevel analysis

of the social entities they belong to (scholars like Auguste Comte have denied that), however it is undeniable that establishing the causality of events is particularly difficult as soon as large populations are involved, and for pragmatic reasons it shall be assumed here that multilevel analysis can indeed clarify causality under certain circumstances. While in a sequence of historical events the association of parameters with each other can readily be detected, the decision about precondition or consequence? - in other words the question of causality - is more difficult to answer.

The explanantia of such an analysis are activities of institutions, organizations or other groups of people with certain characterizing properties. However, purposeful action can only be assumed of individuals or small groups of persons, therefore the application of a general theory of action is only possible at the micro level – the transition between the levels has to follow plausible rules related to the properties of the macro population. Likewise, the causal relation being established at the micro level, this relation has to be translated back to the macro level, following transformation rules. That way, by explaining the selection of actions by individual actors, and aggregation of individual actions to reconstitute the collective explanantia, it is possible to proceed from the original mere *description* of situations by means of bridge hypotheses towards a true *explanation*.

MAX WEBER IN TODAY'S MEDICAL LITERATURE

Apart from his role as one of the founding fathers of sociology, Max Weber made a major contribution to medical methodology when he introduced the validated questionnaire as a diagnostic tool. This achievement is still one of the issues discussed in today's literature with regard to Weber, in addition to psychiatry, theory of ethics and purely historical articles. Weber's approach to methodology was his distinction between "explaining" and "understanding": to explain a phenomenon implies considerations about causality, whereas understanding may be achieved by phenomenological bracketing. While in science a purely phenomenological approach is usually not sufficient, or at least satisfactory, in ethical terms understanding is the method of choice: Explaining certain aspects of, for instance psychiatric disease, may be possible and necessary but trying to "explain" a fellow human in his or her essence is unethical. A recent psychiatric article³ (with response⁴) discusses Weber's influence on psychiatrist and philosopher Karl Jaspers in this regard. In a Swedish article from 2001⁵, Weber is cited as a protagonist of academic freedom and value-free science. In the same year, RM Brain argues that with the questionnaire⁶ approach Weber drew conclusions from his investigations about social measurement and made a tool borrowed not from natural sciences but rather from comparative historical sciences available to sociology and medicine. In 1997 a conference on evaluation of ethics case consultation⁷ was summarized from a Weberian perspective by FD Degnin in the Journal of Clinical Ethics. Earlier articles, still present in medical online databases, deal with mainly historically interesting issues^{8,9} including a 1947 article by EM Manasse about Weber's assumed opinions about race¹⁰.

THE EXPLANANTIA OF MENDELIAN RANDOMIZATION IN MEDICINE

The term „Mendelian randomization“ was coined in 1991 by Gray and Wheatley¹¹, when they conducted an intention-to-treat analysis to compare the outcome of bone marrow transplantation in children with acute myeloid leucemia with conventional therapy. The nature of this rare but severe condition makes it almost impossible to conduct randomized controlled trials, the gold standard to compare treatment options in medicine. There is always a potential conflict in the usual process of randomly assigning patients to one or the other treatment group, since as a matter of principle every patient has to be offered all possible treatment options a medical practitioner has at his or her hands. When they

wanted to compare outcomes of the two treatment options - bone marrow transplantation versus conventional therapy - Gray and Wheatley therefore introduced the new approach of comparing children who actually had a potential bone marrow donor, usually a twin or sibling, with those who had none. The randomization process was not carried out by the researchers conducting the trial, but by the Mendelian process at conception determining whether a patient had a matched sibling donor available or not. The intention-to-treat principle, which is used in all randomized controlled trials, implies that patients should be analysed in the assigned group whether they actually received the intended treatment or not. That way a truly unbiased way of comparing the two treatment options for these patients was established. Over the years, the method was extended and was used in general to reach conclusions about causality in findings of observational association studies. In a letter to the Lancet Martijn Katan¹² introduced the notion that the term „Mendelian randomization“ was applicable whenever genotype-disease associations could be studied as a way of imputing the causal nature of the association between an environmentally influenceable intermediate phenotype and disease. Katan himself applied the method in the early 90ies when the finding of high blood lipid levels being associated with mortality lead to a debate about the causal nature of lipids – were the raised lipid levels indeed causal factors or merely associated risk markers? Analyzing genetically defined populations with polymorphisms leading to inborn hyperlipidemia, Katan could show that mortality from cardiovascular causes was elevated in this population, suggesting a causal relationship. Later another parameter – homocysteine – was found to be non-causal with regard to cardiovascular events. The first example of this approach being used in nephrology was a study about lipoprotein (a) and its role as a risk factor of coronary artery disease in dialysis patients¹³ in 1994. In one of the most recent examples it was applied to studying uric acid and its role as one of the main causal agents in the development of metabolic syndrome¹⁴ – GLUT9, a transporter in the proximal renal tubule, had been identified in a genome wide association study to be the single most important gene locus associated with uric acid serum level variation (p 10 to the power of - 202): comparing sub-populations with genetic polymorphisms of the coding gene an association with the features of metabolic syndrome could be shown. Since causality in these sub-populations is clearly defined due to the monogenetic relationship between genotype and phenotype, going back to the macro level the same causal relation between uric acid and features of metabolic syndrome can be inferred in the interpretation of multi-center association data.

This overview shows how this new method developed gradually during the last 20 years, from the starting point of epidemiological data showing associations of parameters at the macro level. The necessity to make therapy decisions required the clarification of causality though, and the evolving genetic techniques allowing for clear causal explanations at the micro level lead to the development of mendelian randomization as a method. All this happened without any reference to multilevel analysis in sociology or to Max Weber, in fact in the beginning several groups used the same methodological approach independently of each other, so that the term “mendelian randomization” is for instance not even mentioned in the Kronenberg paper of 1994. However, today the method is established in daily medical research routine and displays certain features that can clearly

be described from a methodological perspective: The explanantia of mendelian randomization are disease factors, the relation between measurable parameters in patient cohorts or groups of healthy volunteers with certain characterizing properties. True causal relations with more or less no exogenous confounding factors can only be assumed at the micro level, in genetically defined individuals or small groups of persons, in whom the parameter in question may be explained by the application of the general theory of gene transcription – the transition between the levels again has to follow plausible rules related to the properties of the macro population. Likewise, the causal relation being established at the micro level, this relation has to be translated back to the macro level, following transformation rules. That way, by explaining the relation between certain parameters in individual patients, and aggregation of individual data to reconstitute the collective explanantia, it is possible to proceed from the original mere *description* of associations by means of bridge hypotheses towards a true *explanation*, and the distinction between mere risk markers and actual risk factors of disease.

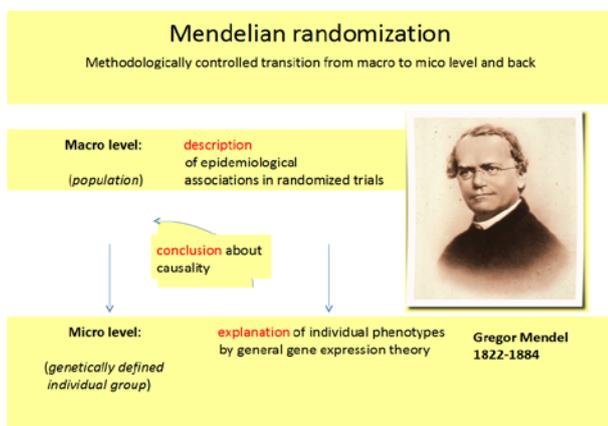


Figure 2: scheme of transitions between macro and micro levels in mendelian randomization

In recent years the method of Mendelian randomization has been developed further and was successfully applied to pharmacogenetics, too: it allows for the discrimination between on-target and off-target effects of a therapeutic agent. Preconditions for a successful application of Mendelian randomization trials are a clearly defined monogenetic causal relationship between a genotype and a phenotype at the micro level of polymorphic sub-populations and clear rules of transition between the micro and macro levels – that way association data at the macro level may be interpreted and intermediate phenotypes be classified as true risk factors or mere risk markers of disease conditions.

CONCLUSION

“Multilevel analysis” appears to be a methodological term characterizing a whole group of methods applicable in different disciplines from economics and sociology to medicine. In all of them the establishment of causal relations is achieved by means of general theories at the micro level. The general theory of action, describing the selection of actions by individual actors (acting purposefully) corresponds

with the general theory of gene transcription in genetically polymorphic individuals (showing genetically determined differences in certain parameters). At the macro level, large groups of people characterized by their role in society correspond with patient cohorts characterized by certain measurable parameters. In both settings, the method can only

Mendelian randomization as an application of Multilevel analysis to medicine		
	<i>Sociology</i>	<i>Medicine</i>
Explanantia:	associated phenomena in society - precondition or consequence?	associated parameters in epidemiological trials - mere risk marker or true risk factor?
Macro level:	institutions or organizations with certain properties	large patient populations with certain properties
<i>Defined transition to the...</i>		
Micro level:	individuals or small groups of persons	individuals or genetically defined polymorphic groups
APPLICATION OF THE	GENERAL ACTION THEORY	GENERAL GENE TRANSCRIPTION THEORY

Figure 3: comparison between multilevel analysis in sociology and medicine

be applied successfully under certain conditions (the availability of monogenetic polymorphisms directly influencing a given parameter – the availability of groups of people acting according to defined values or interests in society).

With the growing awareness of research, problem solving and education being interconnected, it is also getting more and more apparent how health care systems form integral parts of society: methodological similarities between medicine, sociology and economics should be explored further.

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