An interesting observational study by Kollerits et al. (this issue) shows for the first time that adiponectin (ADPN) is a direct predictor of renal disease progression in male patients. As ADPN is a pleiotropic, insulin-sensitizing, anti-inflammatory and vasculo-protective cytokine, these results are apparently counterintuitive with respect to biological effects of this peptide. This study offers a stimulating starting point for discussing the use of observational studies in the complex process of causality assessment and for focusing on the fundamental importance of the clinical context wherein a given risk factor is being tested.

**Observational studies and etiologic research**

The problem of causality is central to clinical medicine. Inferring the cause of a given disease is a creative process based on conjectures and refutations that requires a variety of scientific verifications, including epidemiologic and experimental studies.² The concept of risk factor for the study of multifactorial diseases such as hypertension, atherosclerosis, and chronic kidney disease (CKD) was developed about 50 years ago by investigators of the Framingham study. This concept is now used both to explore the causes of diseases (etiologic research) and to estimate the probability of adverse outcomes (prognostic research). Although based on common statistical techniques, these two types of research are conceptually much different. When we test the association of a putative risk factor — for example, ADPN — as a causal risk factor for renal disease progression (etiologic research), we ought to establish whether this association is independent of other risk factors; that is, we ought to exclude that the association is spurious because of the link of ADPN with other well-known risk factors. To this end, the clinical investigator and the biostatistician construct multivariate models that allow control for confounding by other risk factors. This approach is similar to that applied by a scientist who tests the effect of ADPN in experimental animals. In such an experiment, animals randomly receive either ADPN or an inert substance (control group). If properly performed, an experiment of this kind can isolate the effect of ADPN from other factors, because randomization equalizes both known and unknown risk factors, excluding ADPN, among the experimental animals; that is, randomization produces groups that, on average, have very similar blood pressure, cholesterol, renal function, and so on. When all risk factors are similar, the outcome is determined only by the experimental maneuver, that is, by exposure or lack of exposure to ADPN. Likewise, in prospective cohort studies, multivariate analysis makes it possible to set all known risk factors but the factor being tested at the average value and to adjust the outcome accordingly. It is important to emphasize that, however accurate they can be, observational studies have the obvious, inherent limitation that they cannot control for unknown risk factors, a problem that can be resolved only with randomized experiments. It is worth mentioning that, whereas control for confounding is fundamental in etiologic research, confounders are absolutely not a problem in prognostic

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**Adiponectin and renal disease progression: Another epidemiologic conundrum?**

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In an analysis based on the Mild to Moderate Kidney Disease (MMKD) study, adiponectin, a pleiotropic, insulin-sensitizing, anti-inflammatory and vasculo-protective cytokine, was directly related to renal disease progression. The precise definition of this apparently paradoxical epidemiologic conundrum now requires that the research focus be moved from the study database to the experimental laboratory.


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5. Kollerits B, Nowotny P, Strasser-Weippl S et al. An interesting observational study by association now requires that the research focus be moved from the progression. The precise definition of this apparently paradoxical and vasculo-protective cytokine, was directly related to renal disease study, adiponectin, a pleiotropic, insulin-sensitizing, anti-inflammatory cytokine, these results are apparently counterintuitive with respect to biological effects of this peptide. This study offers a stimulating starting point for discussing the use of observational studies in the complex process of causality assessment and for focusing on the fundamental importance of the clinical context wherein a given risk factor is being tested.

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**T cells and IFN-gamma. J Immunol 2006; 176: 3108–3114.**
Fat mass, body mass index
Inflammation (CRP, IL-6)
Insulin sensitivity
GFR

Adiponectin and clinical outcomes in epidemiologic studies

Figure 1 | Association of adiponectin with other risk factors and clinical outcomes. 
Upper panel: Summary of the relationship between adiponectin (ADPN) and some clinical characteristics. Lower panel: On biological grounds, the expected relationship between ADPN and clinical outcomes is an inverse one. However, this relationship may be confounded in a complex way by the presence of functional correlates of ADPN. Thus, inflammation, malnutrition, and low glomerular filtration rate (GFR) (three obvious risk factors for adverse outcomes) tend to flatten, or even reverse the direction of, the association. However, the confounding effect of the GFR on plasma ADPN may almost completely disappear in end-stage renal disease patients, in whom the GFR nearly equalized to 0. ADPN resistance and secondary (counter-regulatory) hyperadiponectinemia would also tend to reverse this association. The prevalence and the functional effect of ADPN polymorphisms that influence plasma ADPN in the population under study and other factors (for example, prevalence of individuals with insulin resistance) may also influence the relationship between this cytokine and clinical outcomes. The final association depends on the clinical context wherein the association is tested (that is, on the presence or absence and the actual level of confounding variables). CRP, C-reactive protein; IL-6, interleukin-6.

Framing the populating at risk: The experimental context is fundamental
In clinical medicine, some effects observed in a given context are not necessarily seen in other contexts. For example, sympatholytic drugs with weak α1 agonistic activity, such as clonidine, consistently lower blood pressure in hypertensive patients but raise blood pressure in some patients with sympathetic failure and postfunctional norepinephrine supersensitivity. Similarly, in observational studies, a relationship between a predictor variable and an outcome variable in a given population may not be confirmed or may even take an opposite direction in other populations. In individuals free of cardiovascular complications, the relationship between arterial pressure and cardiovascular risk is linear without evidence of a threshold. This relationship goes along with intervention studies showing that reducing the level of blood pressure lowers the risk of disease in hypertensive patients without obvious cardiovascular involvement. Yet, the continuous relationship between blood pressure and cardiovascular events observed in hypertensive patients does not apply to other populations — for example, to populations with preexisting cardiovascular comorbidities. For example, in patients with heart failure, blood pressure is inversely rather than directly related to death. This is because low blood pressure in heart failure is a surrogate of pump failure, and therefore it is associated in an inverse fashion with mortality.

Adiponectin: Lights and shades of epidemiologic studies
ADPN is an adipocyte-derived protein with antiatherogenic and anti-inflammatory properties that is inversely related to fat mass and to body mass index (obese persons produce less ADPN than individuals with normal or low body weight). As is also discussed by Kollerits et al., despite almost indisputable biological evidence that ADPN is a protective factor, prospective epidemiologic studies in the general population and in patients with cardiovascular diseases produced apparently inconsistent results. ADPN is increased in patients with CKD, particularly in those who reach end-stage renal disease. In end-stage renal disease patients, high ADPN predicted a lower risk for cardiovascular events. This association was interpreted as a compensatory response to inflammation and/or malnutrition, an interpretation in keeping with the finding that, independently of the glomerular filtration rate, ADPN is markedly increased also in patients with nephrotic syndrome. Similarly, in other analyses in the same CKD database interrogated by Kollerits et al. (the Mild to Moderate Kidney Disease study database), high ADPN was associated with relatively higher insulin sensitivity and with a lower incident risk for cardiovascular disease, again suggesting a protective effect of this cytokine. In contrast, Menon et al. showed a direct rather than an inverse relationship between ADPN levels and mortality in patients with stage 3 and 4 CKD who took part in the Modification of Diet in Renal Disease study.

These apparently conflicting results highlight some interpretative problems in etiologic research based on epidemiologic studies. Disparate results depend on the particular population being investigated, the case mix, and confounding by other risk factors that may be difficult to control statistically. This is because the measurement
of these covariates is often imprecise, thus leaving substantial residual confounding. For example, in the study by Becker et al., the mean estimated glomerular filtration rate was 63 ml per minute and the mean ADPN 6 μmol per liter, compared with 32 ml per minute and 12 μmol per liter in the study by Menon et al.9 The much lower ADPN in the first of the two studies clearly reflects less severe renal insufficiency. Given the close association between ADPN and renal function, the direct relationship between ADPN and mortality in the study by Menon et al.9 may be due to residual confounding attributable to reduced renal function and/or to confounding by processes that accompany chronic renal diseases that are not captured by adjustment for the glomerular filtration rate. Furthermore, differential retention of high-molecular weight forms of ADPN in renal failure,9 the nutritional and inflammatory status, polymorphisms in the gene encoding ADPN, and the various possibilities of combination of these factors may substantially alter the expected (inverse) relationship between ADPN and clinical outcomes (Figure 1). Causality assessment is a complex process, and epidemiologic associations per se rarely if ever allow definitive conclusions on causality. Biological experiments and randomized experimental studies in animal models and in humans are needed to frame a reliable interpretation of such associations. Yet the study by Kollerits et al.1 is a very intriguing hypothesis-generating exercise, because, in a context where ADPN manifested its insulin-sensitizing and cardiovasculo-protective properties (Becker et al.’s analysis in the same database7), it also displayed a clear-cut direct association with a faster rate of renal disease progression. This is noteworthy because, in general, cardiovascular and renal damage proceed in parallel in patients with CKD.

To explain their counterintuitive findings, Kollerits et al.1 advance the hypothesis that in men with CKD there may be a condition of resistance to ADPN. However, because in this same cohort high ADPN was associated with a lower incident cardiovascular risk,7 this hypothesis would imply that ADPN resistance in CKD patients is confined to the kidney. Medical research during the past century has been a to-and-fro process, from the bench to the bedside and vice versa. Given the therapeutic potential of increasing ADPN by pharmacologic intervention, the definition of the nature of the relationship between ADPN and progression of renal disease is a worthy scientific question. The precise definition of this association now requires that the research focus be moved to the experimental laboratory.

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Malignancy after kidney transplantation: Still a challenge

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Long-term complications of continuous immunosuppression still remain a serious threat and are currently drawing the attention of transplant physicians. Wimmer et al. show that malignancy occurs approximately fourfold more frequently in renal-transplant recipients than in a normal control population. Besides immunosuppression, viruses probably play an important oncogenic role in transplant recipients. The retrospective analysis by Wimmer et al. suggests that mTOR inhibitors and interleukin-2 receptor antibodies are promising immunosuppressive drugs to reduce the risk of cancer after transplantation. These preliminary results must be confirmed in large, prospective, randomized, controlled trials, with long follow-up, designed to evaluate the incidence of de novo malignancy in transplant recipients.


Tremendous progress has been made in the field of clinical transplantation since the first kidney transplantation was performed in 1954.1 Still, transplant physi-