

# Religion, Spirituality, and Mental Health

## Current Controversies and Future Directions

Simon Dein, *FRCPsych, PhD*,\* Christopher C. H. Cook, *FRCPsych, PhD*,†  
and Harold Koenig, *MD, MHSc*‡§

**Abstract:** Although studies examining religion, spirituality, and mental health generally indicate positive associations, there is a need for more sophisticated methodology, greater discrimination between different cultures and traditions, more focus on situated experiences of individuals belonging to particular traditions, and, in particular, greater integration of theological contributions to this area. We suggest priorities for future research based on these considerations.

**Key Words:** Religion, spirituality, mental health, controversies

(*J Nerv Ment Dis* 2012;200: 852–855)

Research on the relationships between religiousness, spirituality, and mental health has burgeoned in the past 20 years. Overall, a preponderance of studies indicates that religious individuals fare better than their secular counterparts in selected psychological disorders (Hackney and Sanders, 2003; Koenig et al., 2012, 2001).

Recent data suggest that religion and spirituality are important coping strategies in those with schizophrenia (Mohr et al., 2011), and for patients with helpful religion, the importance of spirituality was predictive of fewer negative symptoms and better clinical global impression, social functioning, and quality of life (Mohr et al., 2006; Siddle et al., 2002). In relation to depression, surveys in the non-clinical general population and community samples reveal fairly consistent inverse relationships between global indices of religion (e.g., frequency of church attendance and self-rated religiousness) and depressive disorders (Smith et al., 2003). It seems that “religiosity” exerts both a main effect on depressive symptoms and a buffering effect in which religious factors become more salient as life stresses increase. In addition, religion has been reported in several studies to predict a faster remission from depression in those with this disorder (Koenig, 2007). In contrast, the relationships between anxiety and religious involvement seem to be complex, with some studies reporting less anxiety among the more religious, some demonstrating increased anxiety, and others finding no relationship (Shreve-Neiger and Edelstein, 2004).

Rates of drug and alcohol abuse have been found to be significantly lower in those who are religious compared with their nonreligious counterparts (The National Center on Addiction and Substance Abuse at Columbia University, 2001). Substance abuse

has the largest and the most decisive literature on religion and mental health, has longitudinal data, and may underlie a lot of the other findings, so it should be further explored.

Another area that has been extensively covered, mainly in the sociology literature, is the relationship between religion, spirituality, and teenage delinquency. Religious measures are generally inversely related to deviance, and this is especially true among the most rigorous studies (Jackson et al., 2008; Johnson et al., 2000). These authors suggest that the findings indicate that future research on delinquency may gain explanatory power by incorporating religious variables in relevant theoretical models.

It has been asserted, however, that the claims for positive associations between religion and health have been grossly exaggerated (Sloan, 2006; Sloan et al., 1999). This article examines the methodological problems in this field and particularly argues for the need for researchers to incorporate insights into the nature of spirituality and religion derived from anthropology, theology, and religious studies.

### METHODOLOGICAL ISSUES

Researchers deploy diverse definitions and scales of religion and spirituality, upon which the results of empirical studies are highly dependent, but the content of the chosen scales does not always accurately reflect the chosen definitions (Cook, 2004). Religiosity and spirituality are multidimensional constructs (Salsman et al., 2005), and it is necessary to specify exactly which dimensions are assessed in any given study and to have theoretical justification for doing so.

Definitions of nonreligiousness are also problematic. Many studies include samples of individuals classified as “low spirituality” or “religion: none,” with little consideration given to the heterogeneity of these groups (Hwang et al., 2009). Atheism, a belief that there is no God, is arguably more akin to religious belief than nonbelief. In one study, strong atheists were no more likely to be depressed than were strong believers and were less depressed than were weak believers or wavering agnostics (Riley et al., 2005). It may be the strength of belief rather than the type of belief that positively impacts mental health. The small number of self-identified atheists in most populations makes inclusion in research studies in numbers high enough for adequate power quite difficult, and it is even more difficult to control for characteristics (e.g., high level of education, high socioeconomic status) that relate positively to mental health.

True agnosticism, a philosophical commitment to the impossibility of knowing whether there is a God, is much less common than uncertainty about what is believed or failure to reflect on what one does believe. Distinctions are rarely made between atheists/agnostics who self-identify as spiritual and those who eschew any such label.

Some studies do not distinguish between spirituality and religion. Whereas traditional measures of religiosity tend to be more objective based on observable behaviors such as church attendance or frequency of prayer, it is almost impossible to imagine any way of measuring spirituality that is uninfluenced either by religious belief and practice on the one hand or by psychological variables on the other. When spirituality is measured using indicators of good psychological or social well-being, then it cannot meaningfully be said to predict such well-being. Either a more robust and discriminative

\*Research Department, Mental Health Sciences, University College London, London, England; †Department of Theology and Religion, University Durham, Durham, England; ‡Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC; and §Department of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

Simon Dein is an honorary consultant psychiatrist at North Essex Partnership NHS Foundation Trust.

Christopher Cook is the director of the Project for Spirituality, Theology & Health and a professor in the Department of Theology and Religion at Durham University.

Send reprint requests to Simon Dein, FRCPsych, PhD, Research Department, Mental Health Sciences, University College London, Charles Bell House, 67-73 Riding House St, London W1W 7EJ, England. E-mail: s.dein@ucl.ac.uk.

Copyright © 2012 by Lippincott Williams & Wilkins

ISSN: 0022-3018/12/20010-0852

DOI: 10.1097/NMD.0b013e31826b6d1e

methodology for measuring spirituality is needed or research should focus on religious belief, practice, or experience.

Studies are often cross-sectional in design, giving no indication about causality. Many studies have looked at religion and mental health using advanced statistical modeling, although few have been prospective. There are some exceptions. Hill et al. (2006) used growth curve modeling to examine the prospective relationship between religious involvement and cognitive functioning among older Mexican Americans. Respondents who attended church monthly, weekly, and more than weekly tended to exhibit slower rates of cognitive decline than those who did not attend church. In a 10-year prospective study of offspring of depressed and nondepressed patients, Miller et al. (2012) found that a high self-report rating of religion or spirituality may have a protective effect against recurrence of depression, particularly in adults with a history of parental depression.

Religious factors may function in different ways at different times through the life span. Inverse relationships have been found between religiosity and symptoms of depression in children as well as anxiety and psychotic symptoms (Miller et al., 1997). In adolescence, religious involvement exerts salutary effects on subjective well-being, and religious adolescents experience fewer depressive or anxiety symptoms (Regnerus et al., 2003). Few studies, however, follow children through adolescence and into adulthood and later life to see the long-term effects of religious beliefs, practice, and training on mental health across the life span.

One retrospective study has examined how elderly people viewed religious changes during their life course. Qualitative interviews with adults 65 years or older identified four different trajectories of religiosity across the life course: stable, increasing, decreasing, and curvilinear (Ingersoll-Dayton et al., 2002). Consistent with previous studies using retrospective data, the narratives of the older participants emphasized increasing religiosity over time. However, some stories included evidence of decreasing religiosity particularly with respect to organizational participation. Future research should be directed at identifying correlations between such trajectories and mental health.

Although some authors postulate that religious factors directly influence the relationships between religion and mental health (Jones, 2004), others assert that religious variables can be reduced to other factors that have been previously found to influence mental health, more generally: social support, healthy lifestyles, positive emotions, positive appraisals, and effective coping (George et al., 2002). Few studies have incorporated a methodology capable of distinguishing between such direct or indirect causal mechanisms. Most of the studies have not been designed from the start to examine religion-health relationships but have depended on existing data sets that were acquired for some other purpose and seldom have sophisticated measures of religious involvement; the research is based on one or two items someone managed to slip into a larger study, not from specific studies designed for this topic.

Some scholars are more skeptical about religious influences altogether, asserting, rather, that these may be the product of selection effects and social desirability bias in surveys (Regnerus and Smith, 2005). This may be particularly important in relation to studies of religion and drug/alcohol abuse: people with substance abuse problems may be reluctant to participate in religious activity (because of guilt), may be more likely to minimize or deny drug/alcohol abuse, and/or may be excluded from religious activity. People tend to engage in more or less religious behavior for a variety of reasons, including some that have nothing to do with acceptance of particular (orthodox) religious beliefs. Researchers and authors must be careful not to assume that the benefits of religion are related to belief (or, at least, are related to traditional or orthodox belief) and must consider the other reasons why people engage in religious behavior (e.g., social support, conformity, tradition). Certain personality types such as the

“risk averse” may be more likely to be religious and also to lead more healthy lifestyles, hence confounding the relationship between religion and health (Iannaccone, 1995).

## RELIGION AND CULTURE

Anthropology has a long-standing interest in religion, yet few anthropologists have contributed to the literature on religion and mental health. It is a comparative discipline that offers a detailed database of in-depth studies of a wide range of communities that can be compared and contrasted to facilitate an understanding of which patterns of behavior are universal and of which patterns are unique and shaped by local contexts. Ethnographic research provides detailed contextual accounts of religious experiences and practices, giving a voice to those whom we study and allows us to see the world from an emic perspective (from the native's point of view; Ware et al., 1999). We cannot assume that notions of mental health and illness are similar across cultural groups (Kleinman and Benson, 2006). In traditional cultures that emphasize collectivism rather than individualism, selfhood and the spirit world are closely interlinked, with mental health and spiritual health closely reflecting each other. Terms such as *God*, *religion*, *spirituality*, and *belief* are differentially understood cross-culturally, thus signaling the need for detailed ethnographic research and cross-cultural validation of measurement scales.

Culture and religion are inextricably woven together (Geertz, 1973). Specific teachings and observances may be understood differently in diverse cultural contexts, and the salience of various dimensions of religion (ideological, intellectual, social, experiential, and ritualistic) may vary across cultural groups. Numerous studies have demonstrated the influence of these and related constructs on coping with stress, formation of social relationships, occupational attitudes, conflict, life satisfaction, and development of values (Tarakeshwar et al., 2003). Many researchers have drawn attention to the cultural diversity of religious/spiritual coping, appealing for qualitative, multifaceted, cross-cultural designs that can tease out the relative contributions of culture and religion. To date, few researchers have heeded this appeal.

Despite the growing ethnic diversity in North America and Europe, researchers continue to deploy cross-sectional methodologies limited to single-faith samples. There are some exceptions. One study of perspectives on death in Muslim communities in two different countries (Egypt and Bali) found that despite their common religion, members of the two cultures dealt very differently with death (Wikan, 1988).

Furthermore, there is emerging evidence that relationships between religious attendance and mental health may be moderated by ethnicity. In one study of a representative sample of US adults, there were racial/ethnic differences, with Hispanics and African-Americans showing a stronger relationship between attendance and distress than non-Hispanic whites (Tabak and Mickelson, 2009). Thus, future studies on religion and mental health should take account of culture and ethnicity as moderating factors.

Two contemporary areas of anthropological interest might inform the religion and mental health agenda. First, there is a prominent focus in the anthropology of religion on religious experience, its phenomenology, and its relationships to mental well-being that ties together issues of agency, sex, embodiment, and power. Compared with belief and attendance, religious experience has been neglected in the scholarly literature (Dein, 2010). In many cultures, religious rituals and prayer are prevalent strategies for dealing with adversity, but we know little about their mental health consequences. Phenomenological differences between experiences in prayer and psychopathological states are not always clear (Dein and Littlewood, 2007). There may be significant phenomenological overlaps between experiences labeled as psychotic and those labeled as religious (Brett, 2002).

Although much of the ethnographic work on religious experience has focused on “spirit possession” in non-Western cultures (Boddy, 1994), there is some work examining charismatic Christian healing in the United States (Csordas, 1994) and hearing God’s voice among Pentecostal Christians in the United Kingdom (Dein and Littlewood, 2007).

Second, there is now a wealth of anthropological data examining the role of “religious” healing of diverse mental and physical disorders. Although predominantly focused on “traditional” societies, such studies illuminate the ways in which religious factors might facilitate healing in “modern” societies (Watts, 2011).

Finally we cannot assume that findings from one religion can be extrapolated to all religions. Although there has been some recent progress in moving beyond the typical focus on Christianity to examine Judaism, Buddhism, Hinduism, and Islam, more attention is needed on the complex interactions of religion, spirituality, and mental health in different cultures and faith traditions (Milstein et al., 2010).

### THEOLOGY AND RELIGIOUS STUDIES

Theology and religious studies address a broad range of inquiry into the historical and contemporary nature of belief and its impact on ethical norms and behavior, values, meaning and purpose in life, self-understanding, and the grounds for human hope or despair, yet little of this seems to be taken into account in the design and implementation of scientific research.

Perhaps most concerning for scientific research on spirituality and health is the largely unexamined idea that generic understandings of spirituality—devoid of history, specificity, or acknowledged tradition—necessarily have anything at all to do with the actual beliefs, practices, and experiences of “lived” spirituality and religion situated in the diverse cultural and geographical contexts of real people in the world today. A greater engagement is needed with the manifold experiences and aspirations of mental health—service users and of others who self-identify as “religious” or “spiritual.”

There seems to be an implicit syncretistic assumption that all situated spiritualities benefit mental health. If these do, we shall only know this by conducting specific research on specific spiritualities. If we are to conduct research that engages with these loci of primary adherence, we need to read, listen, and observe much more carefully before we begin.

Of course, it is not only theologians or clergy to whom we must listen. Ordinary people, from all religious traditions, do not necessarily believe either the “orthodox” things that official teachings define or the accepted academic consensus of the day on matters of doctrine, belief, or practice. However, theological and spiritual writings from the world’s major faith traditions do represent ways of exploring and understanding spirituality, which most scientific research has hitherto not reflected. For an example of this, we might take Christian prayer.

Research on prayer in relation to mental health has typically relied on relatively simple questionnaire items that depend upon self-report of frequency of prayer (Benda, 2002; Cook et al., 1997; Nooney and Woodrum, 2002). However, the definition of *prayer* is itself a complex issue and can end up sounding very similar to processes that we would normally consider to be psychological or psychotherapeutic rather than spiritual or religious. For example, it has been suggested that prayer is “primary speech... that primordial discourse in which we assert, however, clumsily or eloquently, our own being” (Ulanov and Ulanov, 1985). If prayer is, in fact, this fundamentally psychological, how do we distinguish it from psychotherapeutic processes? How do we know that people know when they are (or are not) doing it? How can we measure when it is being done well or badly?

Undoubtedly, some kind of transcendent reference might play a part in any distinction that might be made between what prayer

is and is not, but herein we find another layer of complexity, for the nature of transcendence is also debatable (Mackey, 2000; Rahner and Vorgrimler, 1983). More importantly, if theological definitions of prayer end up using psychological language, it may prove very difficult to operationalize prayer as distinct from psychological processes, whereas if they end up using theological language, it may prove difficult to operationalize it at all because God (however understood) is not an object amenable to scientific study. Nonetheless, prayer and psychotherapy can look very similar to each other (Cook, 2011), and therapeutic practices such as mindfulness (Mace, 2008), although nontheistic, straddle the boundary between the two.

Although this line of thinking might lead us to pessimism about the feasibility of any scientific research on prayer, we do not think that nihilism is inevitable. Rather, it behooves us to be more explicit about what people are doing when they pray (Brümmer, 2008) and to be more sophisticated in our ability to identify different kinds of prayer. For example, it has been proved possible to correlate personality with different kinds of prayer (Francis and Robbins, 2008), which might, in turn, suggest ways through which research might give more attention to such relationships with mental disorder, or, again, images of God (Francis et al., 2001; MacKenna, 2002)—rather than simply belief in (any kind of) God—might prove more discriminatory of positive and negative influences upon mental health.

In one area of prayer research, however, we wonder whether nihilism might be justified. So-called controlled trials of intercessory prayer (Hodge, 2007) generally not only fail to explore the wealth of literature addressing the nature and variety of prayer according to the world’s major faith traditions but also fail to show any theological awareness of how the design of the study might, in fact, be fundamentally flawed. Is it possible or valid within Christian spirituality to ask God for the healing of one person while simultaneously and implicitly asking that someone else should not be healed? Arguably, it is not. If, then, prayer for any one person who suffers is offered only in the context that God is implored to have mercy on all who suffer, how can any difference between study groups possibly be expected? That such fundamental theological questions have typically not been addressed leaves this research looking very simplistic indeed.

### SUMMARY AND CONCLUSIONS

Although much has been learned about the relationship between religion/spirituality and mental health, this area of study remains to be in its infancy because of problems with measurement, consideration of cultural factors and context, and failure to truly integrate theological perspectives into study design and interpretation of results. We have pointed out areas that, given more attention, might promise significant advances and a better sense of direction in this rapidly growing field. Finally, it is important to point out that the research agenda are constrained by funding and there has been a lack of funding for qualitative research. Although the field of religion and mental health has grown considerably during the past decade, most of the research has been done without any funding support. Adequate sources of funding are essential for conducting high-quality research in the future.

### DISCLOSURES

*The authors declare no conflict of interest.*

### REFERENCES

- Benda BB (2002) Factors associated with rehospitalization among veterans in a substance abuse treatment program. *Psychiatr Serv* 53:1176–1178.
- Boddy J (1994) Spirit possession revisited: Beyond instrumentality. *Annu Rev Anthropol* 23:407–434.

- Brett C (2002) Psychotic and mystical states of being: Connections and distinctions. *Philos Psychiatry Psychol* 9:321–341.
- Brümmer V (2008) *What are we doing when we pray?* (revised ed, pp 186). Aldershot: Ashgate.
- Cook CCH (2004) Addiction and spirituality. *Addiction* 99:539–551.
- Cook CCH (2011) *The philokalia and the inner life: On passions and prayer* (pp 381). Cambridge, England: James Clarke.
- Cook CCH, Goddard D, Westall R (1997) Knowledge and experience of drug use amongst church affiliated young people. *Drug Alcohol Depend* 46:9–17.
- Csordas TJ (1994) *The sacred self: A cultural phenomenology of charismatic healing*. Berkeley, CA: University of California Press.
- Dein S (2010) Judeo-Christian religious experience and psychopathology: The legacy of William James. *Transcult Psychiatry* 47:523–547.
- Dein S, Littlewood R (2007) The voice of God. *Anthropol Med* 14:213–228.
- Francis LJ, Gibson HM, Robbins M (2001) God images and self-worth among adolescents in Scotland. *Ment Health Relig Cult* 4:103–108.
- Francis LJ, Robbins M (2008) Psychological type and prayer preferences: A study among Anglican clergy in the United Kingdom. *Ment Health Relig Cult* 11:67–84.
- Geertz C (1973) Religion as a cultural system. In Geertz C (Ed), *The interpretation of cultures: Selected essays* (pp 87–125). New York: Basic Books.
- George LK, Ellison CG, Larson DB (2002) Explaining the relationships between religious involvement and health. *Psychol Inq* 13:190–200.
- Hackney CH, Sanders GS (2003) Religiosity and mental health: A meta-analysis of recent studies. *J Sci Study Relig* 42:43–55.
- Hill T, Burdette A, Angel J, Angel R (2006) Religious attendance and cognitive functioning among older Mexican Americans. *J Gerontol B Psychol Sci Soc Sci* 61:P3–9.
- Hodge DR (2007) A systematic review of the empirical literature on intercessory prayer. *Res Soc Work Pract* 17:174–187.
- Hwang K, Hammer JH, Cragan RT (2009) Extending religion-health research to secular minorities: Issues and concerns. *J Relig Health* 50:608–622.
- Iannaccone LR (1995) Risk, rationality, and religious portfolios. *Econ Inq* 33:285–295.
- Ingersoll-Dayton B, Krause N, Morgan D (2002) Religious trajectories and transitions over the life course. *Int J Aging Hum Dev* 55:55–70.
- Jackson KM, Sher KJ, Schulenberg JE (2008) Conjoint developmental trajectories of young adult substance use. *Alcohol Clin Exp Res* 32:723–737.
- Johnson B, Li S, Larson D, McCullough M (2000) A systematic review of the religiosity and delinquency literature: A research note. *J Contemp Crim Justice* 16:32–52.
- Jones JW (2004) Religion, health, and the psychology of religion: How the research on religion and health helps us understand religion. *J Relig Health* 43:317–327.
- Kleinman A, Benson P (2006) Anthropology in the clinic: The problem of cultural competency and how to fix it. *PLoS Med* 3:1673–1676.
- Koenig H, King D, Carson V (2012) *Handbook of religion and health* (2nd ed). New York: Oxford University Press.
- Koenig HG (2007) Religion and remission of depression in medical inpatients with heart failure/pulmonary disease. *J Nerv Ment Dis* 195:389–395.
- Koenig HG, McCullough ME, Larson DB (2001) *Handbook of religion and health* (p 712). New York: Oxford.
- Mace C (2008) *Mindfulness and mental health* (p 188). London: Routledge.
- MacKenna C (2002) Self images and God images. *Br J Psychother* 18:325–338.
- Mackey JP (2000) *The critique of theological reason* (p 333). Cambridge, England: Cambridge University Press.
- Miller L, Warner V, Wickramaratne P (1997) Religiosity and depression: Ten-year follow-up of depressed mothers and offspring. *J Am Acad Child Adolesc Psychiatry* 36:1416–1425.
- Miller L, Wickramaratne P, Gameraoff MJ, Sage M, Tenke CE, Weissman MM (2012) Religiosity and major depression in adults at high risk: A ten-year prospective study. *Am J Psychiatry* 169:89–94.
- Milstein G, Manierre A, Yali AM (2010) Psychological care for persons of diverse religions: A collaborative continuum. *Prof Psychol Res Pract* 41:371–381.
- Mohr S, Brandt PY, Borrás L, Gillieron C, Huguélet P (2006) Toward an integration of spirituality and religiousness into the psychosocial dimension of schizophrenia. *Am J Psychiatry* 163:1952–1959.
- Mohr S, Perroud N, Gillieron C, Brandt PY, Rieben I, Borrás L, Huguélet P (2011) Spirituality and religiousness as predictive factors of outcome in schizophrenia and schizo-affective disorders. *Psychiatry Res* 186:177–182.
- Nooney J, Woodrum E (2002) Religious coping and church based social support as predictors of mental health outcomes: Testing a conceptual model. *J Sci Study Relig* 41:359–368.
- Rahner K, Vorgrimler H (1983) *Concise theological dictionary*. London: Burns and Oates.
- Regnerus M, Smith C, Fritsch M (2003) *Religion in the lives of American adolescents: A review of the literature. A research report of the National Study of Youth and Religion, No. 3*. Chapel Hill, NC: University of North Carolina.
- Regnerus MD, Smith C (2005) Selection effects in studies of religious influence. *Rev Relig Res* 47:23–50.
- Riley J, Best S, Charlton BG (2005) Religious believers and strong atheists may both be less depressed than existentially-uncertain people. *QJM* 98:840.
- Salsman JM, Brown TL, Brechting EH, Carlson CR (2005) The link between religion and spirituality and psychological adjustment: The mediating role of optimism and social support. *Pers Soc Psychol Bull* 31:522–535.
- Shreve-Neiger AK, Edelstein BA (2004) Religion and anxiety: A critical review of the literature. *Clin Psychol Rev* 24:379–397.
- Siddle R, Haddock G, Tarrier N, Faragher EB (2002) Religious delusions in patients admitted to hospital with schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* 37:130–138.
- Sloan RP (2006) *Blind faith: The unholy alliance of religion and medicine* (pp 295). New York: St Martin's Press.
- Sloan RP, Bagiella E, Powell T (1999) Religion, spirituality and medicine. *Lancet* 353:664–667.
- Smith TB, McCullough ME, Poll J (2003) Religiousness and depression: Evidence for a main effect and the moderating influence of stressful life events. *Psychol Bull* 129:614–636.
- Tabak MA, Mickelson KD (2009) Religious service attendance and distress: The moderating role of stressful life events and race/ethnicity. *Sociol Relig* 70:49–64.
- Tarakeshwar N, Stanton J, Pargament KI (2003) Religion: An overlooked dimension in cross-cultural psychology. *J Cross Cult Psychol* 34:377–394.
- The National Center on Addiction and Substance Abuse at Columbia University (2001) *So help me God: Substance abuse, religion and spirituality*. New York: Columbia University.
- Ulanov A, Ulanov B (1985) *Primary speech: A psychology of prayer* (p 178). London: SCM.
- Ware NC, Tugenberg T, Dickey B, McHorney CA (1999) An ethnographic study of the meaning of continuity of care in mental health services. *Psychiatr Serv* 50:395–400.
- Watts F (2011) *Spiritual healing: Scientific and religious perspectives* (p 207). Cambridge, England: Cambridge University Press.
- Wikan U (1988) Bereavement and loss in two Muslim communities: Egypt and Bali compared. *Soc Sci Med* 27:451–460.