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A biological, latent variable model of health (EarlyBird 68)

Michael E. Hyland, School of Psychology, Plymouth University,

Alison N. Jeffery, Plymouth University Peninsula Schools of Medicine and Dentistry,
Plymouth University

Terence J. Wilkin, Institute of Health Research, University of Exeter

Running head: biological health

Correspondence: Michael Hyland, School of Psychology, Plymouth University, Plymouth
PL4 8AA. Email: mhyland@plymouth.ac.uk

Abstract

Objective: To determine whether factor analysis of a set of health-related biomarkers provides evidence of an underlying common dimension of variation, and to explore the relationship between this dimension of variation with positive and negative affect.

Method: Twelve health-related metabolic, immune and body-composition biomarkers at ages 5, 7, 9, 11, 14 and 16 years were obtained from the EarlyBird longitudinal cohort of 347 children and supplemented by positive affect (PA) and negative affect (NA) measured at age 16 years.

Results: At each age, principal factor analysis revealed that nine of the 12 biomarkers consistently loaded on the first extracted factor, accounting for 25% of the variance at age 5, and 37-44% of the variance at 7 – 16 years. High loading biomarkers included physical indicators of adiposity, insulin resistance, C-reactive protein, triglycerides, and cholesterol. Factor scores at different ages correlated between .48 and .85. Correlations between the first factor scores and mood measured at age 16 were $r = -.17$ ($p = .02$) for PA and $r = .13$ ($p = .07$) for NA.

Conclusions: There is a latent variable, h , that accounts for about a third of the variance of a set of health related physical and biochemical biomarkers. h is comparatively stable during childhood and is a weak predictor of mood. These data provide a rationale for aggregating biomarkers in psychoneuroimmunological research. The concept of h provides a possible

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biological rationale for the role of common factors in disease onset and progression, mental illness, and functional disorders.

Keywords: Health, biomarkers, mood, factor analysis, model

Introduction

The concept of health differs from that of disease in three ways. First, health is treated as a single concept which varies only between good and bad health, i.e., there are not many kinds of ‘good health’. Second, health is not merely the absence of disease but something else. The widely influential World Health Organisation’s definition of health is that Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (WHO, 1948). The exact meaning of ‘mental and social well-being’ can be interpreted in several ways as can the term ‘a complete state’. Third, health is not defined in terms of a biological substrate. Whereas disease is frequently defined in terms of an underlying pathophysiology, health is not – though there are normative ranges for most biological measures that are normally assumed as ‘healthy.’ However, if health is a state, there must be some form of underlying biology that defines the state of health. If materialism is assumed, then there must be an underlying biological substrate to health.

Health status can be measured by several subjective scales that have labels such as health, well-being, quality of life, health related quality of life, happiness and life satisfaction. Correlations between these different scales are high (Pavot & Diener, 1993, 2008), and the conceptual difference between them is not always clear. For example, the labels *health status*, *quality of life* and *health related quality of life* are sometimes used inter-changeably. Subjective measures of health status correlate with trait mood. It is common to distinguish between two types of mood, positive affect (PA), which in its trait form correlates with extraversion, and negative affect (NA) which in its trait form correlates with neuroticism. For both theoretical and empirical reasons, PA and NA are considered orthogonal (Tellegen, Watson & Clark, 1988) as are extraversion and neuroticism (Digman, 1990). Both PA and NA have been shown to correlate with health outcomes – or, more correctly, absence of disease states (Consedine & Moskowitz, 2007; Pressman & Cohen, 2005; Steptoe, Dockray & Wardle, 2009) as do extraversion and neuroticism (Friedman & Booth-Kewley, 1987).

Most measures of life satisfaction and scales of well-being correlate with both PA and NA (Pavot & Diner, 2008). However, although quality of life is commonly defined both in terms of positives and negatives (Sirgy, 2012), health-related quality of life scales, whether generic or disease specific, measure only the adverse effects of illness on the person and correlate only with NA (Hyland, 1992). Some other health status questionnaires also assess only negativity. For example, the General Health Questionnaire (GHQ) measures only the adverse effects of health and is strongly correlated with neuroticism (Goldberg & Williams, 2006). The negatively worded items of the GHQ are psychometrically distinct from equivalent, positively worded items devised by the authors (Huppert & Whittington, 2003).

Although disease states are associated with absence of well-being, positive consequences of illness are reported (Sodergren & Hyland, 2000). Positive interpretations of illness are associated with the personality dimensions of extraversion and openness (Sodergren, Hyland, Crawford & Partridge, 2004) and predict recovery from disease (Hyland, Sodergren & Lewith, 2006). In sum, disease has consequences for both negativity and positivity, whereas

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with the exception of life satisfaction and well-being questionnaires, health status scales assess only the absence of negative consequences of health.

The lack of a biological model of health means that it is unclear whether biological health relates to both PA and NA only to NA or only to PA. The purpose of this paper is to show that it is possible to develop a biological concept of health – in contrast to absence of disease – and to determine to what extent this biologically derived concept correlates with PA and NA.

Over the last 40 years, psychological measures of mood, well-being and happiness have been shown to correlate with a large number of biochemical and physical biomarkers (Segerstrom & Miller, 2004). These biomarkers are inter-correlated between themselves and often involve (sometimes inter-connected) inflammatory mechanisms. Inflammatory mechanisms are associated with a wide range of diseases (Kemeny & Schedlowski, 2007). However, although the correlation between biomarkers and subjective indicators is well established, the correlations are typically small (being in the order of .2 or less) and not always consistent across studies. Additionally, there is little specificity between patterns of biomarkers and specific psychological states of well-being. It is therefore not possible to define health in terms of any one specific biomarker or pattern of biomarkers. Whereas disease often has a specific pathophysiology, health has no specific biomarkers.

We propose that there is no one biomarker that represents biological health. Instead health is a latent variable, h , that is responsible for the inter-correlations between biomarkers, and that this latent variable may also have a causal role in measures of health status. The concept of h should be considered both conceptually and statistically equivalent to the concept of general intelligence, g . The aim of this paper is to carry out a factor analysis on metabolic biomarkers that are conventionally accepted biological indicators of health. We carry out this factor analysis on several sets of data collected over a child's life between the ages of five and 16 years and examine the consistency of the underlying factor structure and factor scores over time and their relationship to PA and NA measured at age 16 years.

Method

Participants: EarlyBird is a prospective, non-intervention cohort study of 307 healthy children from randomly selected schools, based in the city of Plymouth, UK. Mean age at recruitment was 4.9 years. An additional 40 children (3 boys) aged 9y were recruited when the original cohort was aged 9y, to replace some children who had left and to redress the gender imbalance, giving a total cohort of 347 children (173 boys).

The majority (97%) are white European, with a wide socio-economic mix; mean Index of Multiple Deprivation (Noble et al., 2004) is 21.7, range 6.5-73.0; UK mean 26.3). The protocol has been described in detail elsewhere (Voss et al., 2003).

Written consent of the parent, and assent from the child at each visit was obtained. Ethical approval was granted in 1999. The study was conducted according to the principles expressed in the Declaration of Helsinki.

Annual Measures

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Anthropometric measures: Height was measured to nearest mm (Leicester stadiometer, Child Growth Foundation, London). Weight to nearest 100g (Tanita Solar 1632W electronic scales, Tanita Ltd, Middlesex, UK). Body mass index was calculated (kg/m^2) and standardised for age and gender (standard deviation score; BMI sds), according to UK 1990 standards (Cole, Freeman & Preece, 1995).

Skinfold thickness at five sites (biceps, triceps, subscapular, suprailiac and para-umbilical; total in mm; SSF) by skinfold calipers (Holtain Ltd, Crosswell, Crymych, Pembrokeshire).

Waist Circumference: (measured at the narrowest part between the lower border of the ribs and the upper border of the pelvis), by metal tape measure (Chasmors Ltd, London).

A minimum of two 'blind' repeats were made of height, skinfolds and circumferences at each visit and the mean used.

Percent body fat (% fat) measured by dual-energy-x-ray-absorptiometry (Lunar Prodigy Advanced fan beam system, Lunar Corporation, Madison, WI) (from 7y onwards).

Blood pressure was measured by semi-automated sphygmomanometer (Welch-Allyn, Beaverton, Oregon, US), with the participant seated and rested. The mean of the second and third of three recordings of systolic and diastolic (SBP, DBP) were used.

Metabolic profile:

All blood tests were taken fasting between 0900 and 0945.

Insulin was measured by immunometric assay on a DPC Immulite analyser, using kits measured by Diagnostic Products Corporation (Los Angeles, CA). Insulin cross-reactivity with proinsulin was less than 1%, and the detection limit of the assay was 2.0 mU/l.

Glucose, total cholesterol, HDL cholesterol (HDL-C, total cholesterol to HDL ratio (CHR) and triglycerides were measured on a Cobas Integra 700 analyser (Roche Diagnostics, Lewes, UK).

Serum for insulin and high-sensitivity C-reactive protein (CRP) was frozen at -80°C and analysed in batches. Inter-assay sensitivity for insulin 8.0% (mean 2.87 mU/l, SD 0.23) and for CRP <5%. The lower detection limit for CRP assay was 0.1 mg/l, insulin 2 mU/l. Insulin resistance was determined by homeostasis model assessment (HOMA-IR program) (Matthews et al, 1985). HOMA has been well validated in children against clamps with correlations of $r \geq 0.9$ (Gungor, Saad, Janosky & Arslanian, 2004).

Physical activity: MTI (formerly CSA) accelerometers (Fort Walton Beach, FL) recorded clock time, intensity, and duration of physical activity. The accelerometers were worn around the waist for seven days each year. Results are presented as average number of minutes of total physical activity (TPA) recorded per day, adjusted for season.

Twelve biomarkers (BMI sds, SSF, waist circumference, % fat, HOMA-IR, CRP, triglycerides, CHR, HDL-C, SBP, DBP, TPA) were chosen as possible indicators of biological health and were analysed at ages five, seven, nine, 11, 14, and 16 years.

Mood: Mood was measured by the PANAS-C, a scale measuring positive and negative affect that has been validated for use with children (Laurent et al., 1999). In this study, we provide measures of negative affect (NA) and positive affect (PA). In addition, as some authors suggest that mood is a uni-dimensional construct (e.g., Tay & Diener, 2011) we constructed a uni-dimensional measure of Total Mood by subtracting the NA score from the PA score.

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PANAS-C was measured at age 16. The questionnaire was completed by every child in the research centre. Parents gave written consent for their child, but were not present while he or she completed the questionnaire. Children were asked to respond to each adjective on the basis of “How do you normally feel.” The same researcher (AJ) was present on each occasion, and checked the questionnaire for completeness after the child had left the room. If any value was missed the child was asked to answer that question before leaving the research centre (thus there were no missing values). Two children (one girl, one boy) had known psychological problems (eating disorders), and they were excluded from this study at the outset.

Statistics: The variables SSF, waist, % fat, IR, CRP and triglycerides were skewed in distribution and logged for analysis. At each age, exploratory principal axis factor analysis (without rotation) was used to identify dimensions of common variance (latent variables) in the measured variables. The percentage variance for each extracted factor was calculated from eigenvalues. Pearson’s correlations determined relationships between the three mood measures and factor scores from the first unrotated factor in each of the factor analyses.

Results

Exploratory principal axis factor analysis was carried out on the 12 biomarkers at each age, see Table 1 (Note: blanks in the table indicate that a particular biomarker was not measured at that age). A scree plot for the analysis at each age provided evidence of a large first factor, explaining between 25% and 44% of the total variance depending on the age of measurement. Percentage variance for the first unrotated five factors is shown in Table 1. Three of the 12 biomarkers failed to load consistently across the different ages, namely the two measures of blood pressure and the measure of physical activity. All other biomarkers provided evidence of loadings $> .3$ at most ages.

Table 2 shows the correlations between the factor scores of the first extracted factor of the biomarkers at each age and PA, NA and Total Mood taken at age 16. Correlations between the first factor scores are high, but there is a trend for the correlation to decrease with increasing age difference. PA measured at age 16 years correlated with the first factor scores at ages 14 and 16 years. However, NA failed to correlate significantly, though there is a trend (significant at the 10% level) in the expected direction.

Discussion

We demonstrated the existence of a strong first factor that contributed common variance to 9 of the 12 biomarker measures. These 9 biomarkers included physical measures of adiposity as well as biochemical measures, all of which are linked to non-specific inflammatory mechanisms. Factor loadings at ages 7, 9, 11, 14 and 16 years tended to be higher than those at five years, suggesting that the stability of this first latent variable increases over time. The factor analytic data provides evidence for the existence of a construct that we have labelled *biological health*, or *h*. Factor scores of that first factor obtained at different ages were strongly inter-correlated. Although *h* is comparatively stable, it does appear to change as a function of time over a period 11 years. Nevertheless, *h* at age 5 predicts *h* at age 16 years.

Total physical activity loaded $>.3$ only at age 11 years, though some loadings approached that figure at other ages. Total physical activity has been shown to be a consequence not a cause

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of adiposity (Metcalf, Hosking, Jeffery, Voss, Henley & Wilkin, 2011). There was little evidence that systolic blood pressure was related to h , and diastolic blood pressure loaded $>.3$ only at age 7, though some loadings approached this figure at other ages. The reason for the poor relationship between blood pressure and h is unknown. It may be that the relative contribution of different biomarkers to h varies as a function of age.

The latent variable, or h , at ages 14 and 16 years correlated significantly with PA and Total Mood at 16 years. Although h did not correlate significantly with NA at 14 and 16 years, the correlation coefficient was consistent across the period studied and similar in magnitude to that with PA. Our data indicate that h has a weak correlation with mood but no firm conclusion can be reached with regard to the relative association with NA or PA.

Limitations of the study may explain the weakness of the correlation between h and mood. Mood was measured at only one time point, during puberty, and during the year when external examinations take place. In addition, while mood is correlated with subjective measures of health, the two are not equivalent. Finally, the discriminant validity of the PANAS-C has been criticised with regard to social anxiety – which may be particularly high in this population (Laurent et al., 1999), and the theoretical basis for distinguishing positive versus negative affect is not universally accepted (Tay & Diener, 2011). The study was limited by the biomarkers studied. A much more extensive range would be needed to investigate additional dimensions of variance beyond the first factor. A final limitation was that the study population was of Caucasian origin only, limiting generalisability to other populations. Despite these limitations, our data are consistent with data demonstrating the importance of positivity to diseases that have inflammatory component (Boehm, & Kubzansky, 2012; Bostock, Hamer, Wawrzyniak, Mitchell, & Steptoe, 2011; Steptoe, Demakakos, de Oliveira, & Wardle, 2012).

Theoretical implications and an alternative to the WHO concept of health

The WHO model of health is dualist and treats health as form of variation that is separate from disease. While this model is widely respected, it is inconsistent with some data (e.g., the role of poor health as predictor of disease onset; the continuity of symptoms between health and disease states). This section provides a model of biological health that links the concepts of health and disease.

The factor analytic evidence indicates that multiple biomarkers covary along a primary dimension, a dimension we have labelled h . These biomarkers are also indicators of disease risk across a range of different diseases. We propose that h represents variation along a dimension of systemic dysregulation which includes but is not limited to inflammation.

The body can be described as a widely *distributed system* with multiple and strong causal connections forming a complex network of interconnections. It can also be described as a series of separate, *local systems* (e.g., gastric, respiratory, cardiac, immune), each with numerous within-system causal connections. These two descriptions can be combined: The body is a distributed network of multiple causal connections but with areas of localism (see Figure 1). In our model, h represents one of several possible dimensions of dysregulation in the distributed system. Disease is associated with pathophysiology in the local systems.

Fetal distress leads to in utero programming that predisposes to later multiple disease onset (Barker, Bagby & Hanson, 2006; De Boo & Harding, 2006) as well as psychological disturbance (Räikkönen et al., 2008). Adverse childhood experiences (e.g., trauma and abuse)

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lead to epigenetic programming that increase the risk of multiple disease states as well as behavioural changes that may also predispose to disease (Miller, Chen, & Parker, 2011). In sum, existing evidence shows that the body becomes programmed by events throughout the life cycle. We propose that these events and the consequent body programming fall along a primary dimension of benign versus adverse experiences and that this programming is represented in the distributed system. That is, h represents a dimension of epigenetic and other biological changes by which the body encodes information about adverse versus benign life events.

Figure 2 shows a model in which variation within the distributed system, including h , is programmed by life events. Poor h , including non-specific inflammation as well as other dimensions of dysregulation, then predisposes to multiple disease states across several local systems. The local systems are causally embedded within the distributed system, and therefore the causal relationship between the distributed and local systems is shown as bidirectional. Symptoms arise both because of error in the local systems as well as dysregulation in the distributed system. In particular, dysphoric psychological states arise from patterns of dysregulation in the distributed system.

Figure 2 provides a model that is consistent with several types of established data, data unexplained by the WHO model. The biological model is consistent with the observation that multiple diseases share common risk factors (e.g., stress) (Kemeny, & Schedlowski, 2007; Segerstrom & Miller, 2004) and, as proposed by the overspill hypothesis, that specific inflammation can contribute to systemic inflammation (Sinden & Stockley, 2010). The model explains the frequency of co-morbidities in disease states (Needham, Scales, Laupacis, & Pronovost, 2005), as a consequence of h . h explains why dysphoric psychological states (e.g., depression, anxiety, fatigue) inter-correlate and why the ‘disease prone personality’ predicts the onset of multiple diseases (Friedman, 2008; Friedman & Booth-Kewley, 1987). The model is consistent with the observation that psychological states such as depression predict faster disease progression across several diseases (de Voogd et al., 2009; Satin, Linden, & Phillips, 2009), because of a systemic pro-inflammatory profile associated with h .

The biological model of health proposes the existence of h as a primary dimension of variation but other dimensions of variation must also exist in the distributed system. Together, these different forms of dysregulation provide a theoretical basis for types of mental illness where no unique biological basis has been identified (Lacasse & Leo, 2005), as well as the important role stress has in the development of depression (Stroud, Davila, Hammen, & Vrshek-Schallhorn, 2011). The existence of dysregulation within a distributed system also provides a possible theoretical rationale for medically unexplained symptoms and functional disorders. Patients with functional disorders (e.g., irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia) exhibit life altering symptoms without evidence of specific pathophysiology – i.e., without a disease diagnosis – but have abnormalities across a range of different biomarkers, including a raised pro-inflammatory profile and hypothalamic-pituitary-adrenal abnormalities (Henningsen, Zipfel, & Herzog, 2007). Patients are multi-symptomatic and there is considerable overlap in symptoms between different disorders (Aaron, & Buchwald, 2001). Patients with different disorders respond to similar psychological/lifestyle interventions but only poorly to pharmacological interventions (Henningsen et al. 2007), and the disorders may be variations along dimensions of symptomatology rather than discrete disorders (Aaron, & Buchwald, 2001). These characteristics are all consistent with a widely distributed system that varies along several

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dimensions of dysregulation, and where dysregulation is influenced in both directions by lifestyle events.

Conclusions

Two conclusions can be drawn from our data. First, our data provide a rationale for aggregating across several different kinds of biomarkers in biopsychological research. Second, existence of the latent variable, h , implies the existence of a causal system that is distributed throughout the body. We propose that a distributed system varies in terms of systemic dysregulation along the dimension identified by h , but also along other possible dimensions of dysregulation not explored in this paper. The concept of systemic dysregulation provides a way of describing health that (a) shows how it can vary independently of disease and (b) how health is causally linked in both directions with disease as well as being influenced by lifestyle.

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Table 1. First factor loadings from unrotated principal axis factor analysis, and percentage variance explained by the first five unrotated factors.

| Biomarker | 5y | 7y | 9y | 11y | 14y | 16y |
|----------------------|-------|-------|-------|-------|-------|-------|
| BMI sds | .81 | .92 | .88 | .91 | .89 | .86 |
| Log SSF | .71 | .93 | .93 | .93 | .91 | .88 |
| Ln waist | .86 | .86 | .87 | .90 | .88 | .86 |
| Ln % fat | - | .92 | .88 | .89 | .81 | .76 |
| Ln IR | .23 | .50 | .55 | .58 | .48 | .45 |
| Ln CRP | .20 | .40 | .39 | .54 | .38 | - |
| Ln trigs | .40 | .37 | .48 | .56 | .51 | .56 |
| CHR | .44 | .33 | .54 | .56 | .63 | .67 |
| HDL-C | -.37 | -.28 | -.41 | -.53 | -.47 | -.41 |
| SBP | .12 | .06 | -.21 | .01 | .18 | .21 |
| DBP | .17 | .32 | .09 | .29 | .21 | .28 |
| TPA | .02 | -.27 | -.15 | -.32 | -.27 | -.17 |
| % variance explained | 25.34 | 36.73 | 38.39 | 43.72 | 39.00 | 38.66 |

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|---------------|-------|-------|-------|-------|-------|-------|
| by first five | 18.29 | 15.41 | 14.82 | 12.80 | 13.82 | 15.53 |
| extracted | 11.68 | 8.95 | 9.75 | 10.24 | 11.73 | 12.96 |
| factors | 9.28 | 8.39 | 8.54 | 7.73 | 9.86 | 9.60 |
| | 9.05 | 8.18 | 7.46 | 6.50 | 6.06 | 7.00 |

Key

| | |
|----------|--|
| BMI sds | Body mass index (weight in kg/height in m ²) standard deviation score |
| Log SSF | Log ¹⁰ sum of 5 skinfolds |
| Ln waist | Natural log waist circumference |
| Ln % fat | Natural log total fat % from DEXA |
| Ln IR | Natural log of insulin resistance (HOMA-IR) |
| Ln CRP | Natural log high sensitivity C-reactive protein (values ≥ 8 excluded as thought to be related to acute infection) |
| Ln trigs | Natural log triglycerides |
| CHR | Total cholesterol/HDL ratio |
| HDL-C | High density lipoprotein cholesterol |
| SBP | Systolic blood pressure |
| DBP | Diastolic blood pressure |
| TPA | Total physical activity (counts per day) |

Note: blank spaces indicate the measure was not taken at that age.

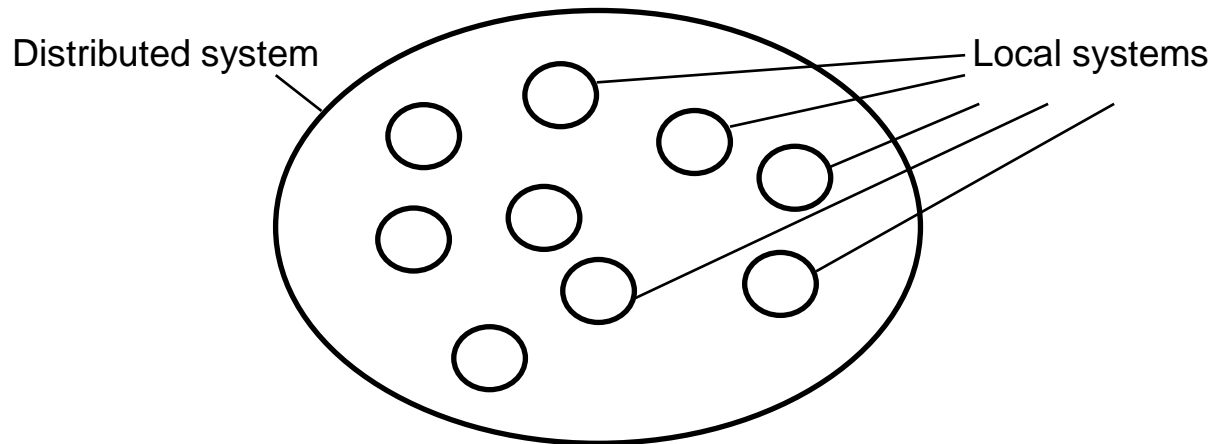
Table 2. Pearson's correlations (p values shown in brackets) between first factor (FS) scores at different ages (in years) and between these factor scores and PA, NA and mood at age 16 years.

| | FS age 5 (p) | FS age 7 (p) | FS age 9 (p) | FS age 11 (p) | FS age 14 (p) | FS age 16 (p) |
|----------------|-----------------|-----------------|-----------------|------------------|------------------|------------------|
| n variables | 11 | 12 | 12 | 12 | 12 | 11 |
| PA age 16 | -.08 (.282) | -.08 (.331) | -.09 (.296) | -.06 (.465) | -.15 (.032) | -.17 (.022) |
| NA age 16 | .14 (.060) | .05 (.577) | .20 (.022) | .10 (.268) | .12 (.072) | .13 (.070) |
| Total | -.13(.082) | -.09 (.292) | -.17 (.054) | -.11 (.222) | -.16 (.016) | -.19 (.011) |
| Mood age 16 | | | | | | |
| FS age 5 | - | .85 | .58 | .70 | .57 | .60 |
| FS age 7 | | | .62 | .83 | .70 | .68 |
| FS age 9 | | | | .56 | .58 | .60 |
| FS age 11 | | | | | .77 | .69 |
| FS age 14 | | | | | | .74 |

Note: p values are shown in brackets, unless the correlation is significant $p < .001$

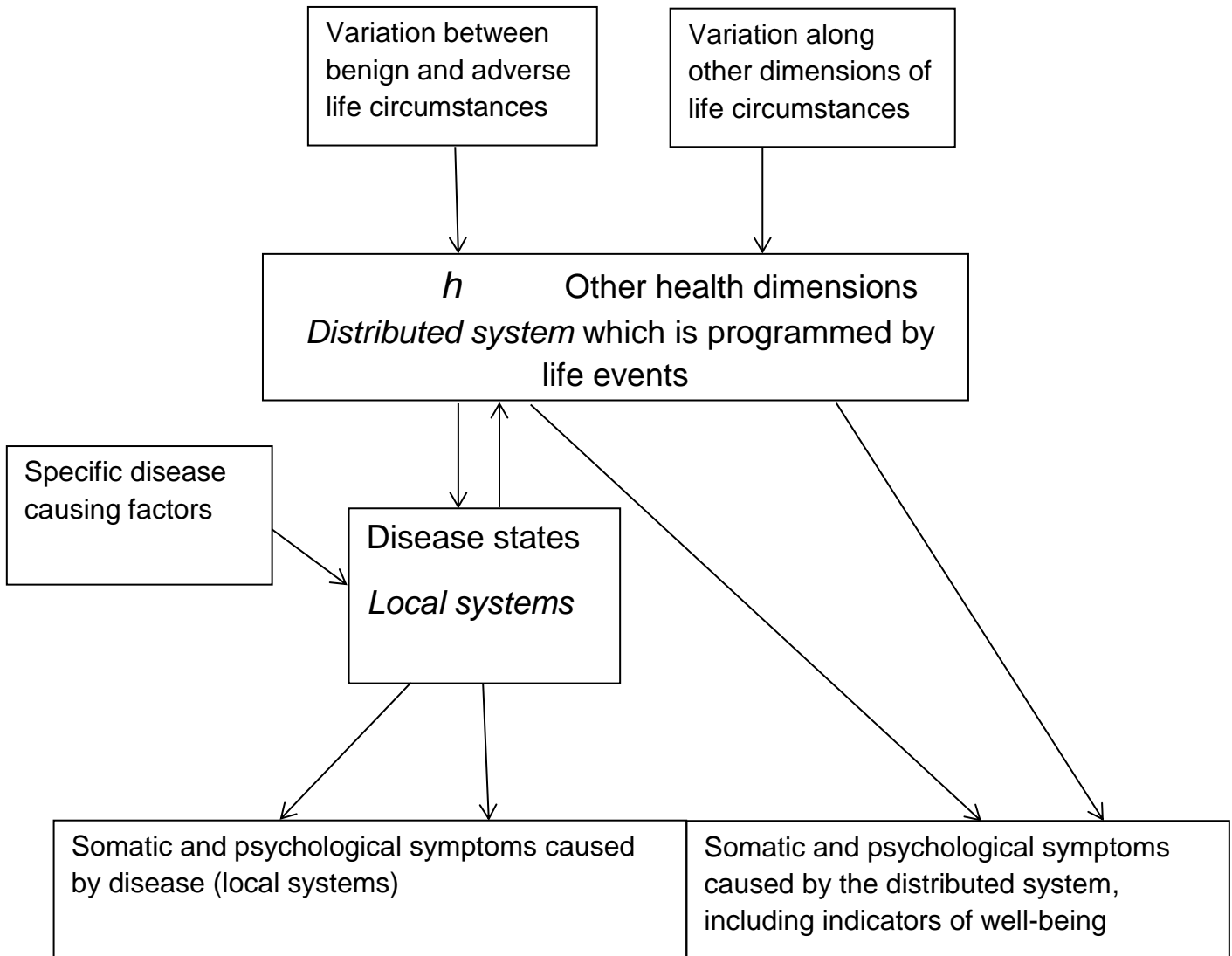
Biological Health

Figure 1. Health conceptualised as a dysregulation within a distributed system and disease as error within a local system.



Note: the local systems are causally connected to and form areas of localisation within the distributed system.

Figure 2. Conceptual model of biological health and disease.



Note: Health is represented by a distributed biological system that is programmed by life events. Health varies along several dimensions, of which *h* explains the most variance and reflects variation between adverse and benign circumstances. The health and disease systems have a bidirectional causal relationship and both health and disease systems cause somatic and psychological symptoms.