Nutrition, Metabolism & Cardiovascular Diseases (2013) xx, 1–8

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Nutrition, Metabolism & Cardiovascular Diseases

REVIEW

Left ventricular geometry in obesity: Is it what we expect?

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Received 6 April 2013; received in revised form 17 June 2013; accepted 27 June 2013

KEYWORDS
Body composition;
Body size;
Allometric signal;
Cardiac geometry;
Cardiac workload

Abstract Obesity is characterized by the disproportionate growth of the components of body size, including adipose tissue and lean body mass. Left ventricular (LV) hypertrophy often develops, due to the coexistence of hemodynamic (cardiac workload) and non-hemodynamic components (including body composition and activity of visceral fat). While the hypertrophy of cardiomyocytes is produced by the hemodynamic load, through sarcomeric replication, there is a parallel growth of non-muscular myocardial components, including interstitial fat infiltration and accumulation of triglycerides in the contractile elements, which are thought to influence LV geometric pattern. Thus, pure intervention on hemodynamic load is unlikely to result in effective reduction of LV hypertrophy in obese. We review pathophysiology and prevalence of LV hypertrophy in obesity, with specific attention to LV geometric abnormalities and relations with body size.

Obesity is the disproportionate growth of components of body size including adipose tissue and lean body mass, characterized by a substantial increase of their ratio [1] and alteration of body composition, which can reach the level of a relative sarcopenia [2]. In relation to the body distribution, adipose tissue presents different physiological characteristics and metabolic activity. Subcutaneous fat is almost metabolically silent and does not require substantial blood supply, whereas visceral fat, including abdominal, mediastinal and epicardial adipose tissue, is metabolically active and requires as much energy support as lean body mass, to produce a number of compounds with autocrine, paracrine and endocrine activities, influencing metabolism and cardiovascular system [3,4].

Pathophysiology of LV hypertrophy in obesity

Hemodynamic mechanisms (Fig. 1)

Because for the energy requirements visceral fat requires a high blood minute supply, compared to normal-weight

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http://dx.doi.org/10.1016/j.numecd.2013.06.012

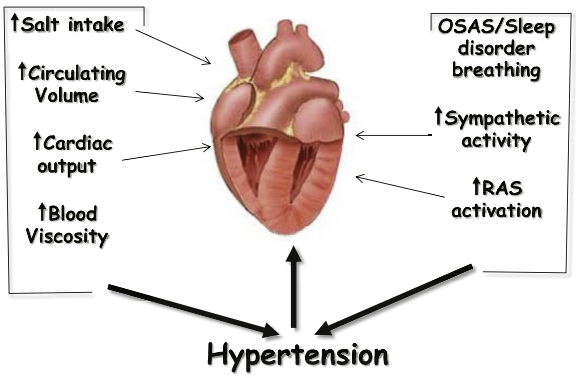

Figure 1 Hemodynamic determinants of LV hypertrophy in obesity. Increase in salt intake, circulating volume, cardiac output and blood viscosity, as well as sleep apnea syndrome (OSAS), sympathetic overdrive and renin angiotensin aldosterone (RAS) systems may cause LV hypertrophy through development of arterial hypertension or even directly.

individuals, the cardiac workload in visceral obesity is constantly increased [5—7]. This increase occurs as a consequence of both increased heart rate and stroke work [7], due to both volume overload and inadequate adaptation of peripheral resistance to the increased output [6]. Stroke work is the most powerful stimulus to increasing LV mass [8] and in obese individuals LV mass is in fact increased [9,10] (Fig. 2).

The biological mechanisms linking the hemodynamic overload with the obesity-related myocardial geometric abnormalities are complex and not entirely clarified. Hemodynamic of obesity is characterized by a predominant volume overload with various degrees of pressure overload related to the degree of increase in blood pressure, near constant, even in the presence of normotension [11]. One of the components of the expanding circulating volume in obesity is the increased salt intake associated with food overload, causing increased water retention [12,13]. In addition, dietary salt intake is also associated with increased myocardial thickness and left ventricular mass [14,15], even independently of blood pressure.

The physiologic response of the renin—angiotensin system to the saline load is altered in young normotensive obese subjects, compared to normal-weight peers [16]: suppression of plasma renin activity (PRA) and aldosterone after salt loading, as well as the consequent increased urinary sodium excretion are significantly reduced or delayed in insulin-resistant obese, compared to normal-weight subjects [17].

Being LV hypertrophy the most potent predictor of cardiovascular disease after age, the link between sodium turnover and LV mass might at least in part explain the association of salt intake with increased risk of stroke and cardiovascular disease [18].

Non-hemodynamic mechanisms (Fig. 3)

The increase in LV mass is particularly linked to central fat distribution [19]. Accumulation of visceral fat is thought to affect signaling, transcription and remodeling of the heart [20]. Visceral adipose tissue promotes a cascade of biological events, including increased availability of angiotensinogen, increased production of proteins with hemodynamic impact (leptin, resistin, adipsin), reduced adiponectin and expression of a number of cytokines with direct inflammatory effect (TNF and IL6 family especially) [3,4]. Furthermore, human adipocytes also produce potent mineralocorticoid-releasing factors [21], which are likely associated with development of arterial hypertension and with enhanced pro-fibrotic activity [22].

Visceral adiposity also generates insulin resistance [23] and stimulates sympathetic drive [5], other potent stimuli for increasing LV mass [24,25]. However, though hyperinsulinemia and insulin resistance have been reported to be associated with LV mass in selected normotensive or hypertensive population samples [25], we could not demonstrate a clear independent association in the Strong Heart

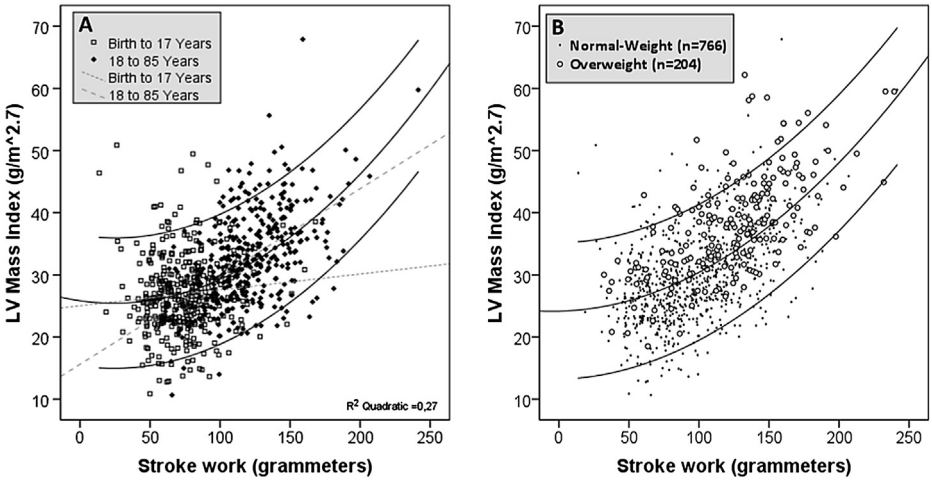

Figure 2 *Panel A*: relation between stroke work and LV mass index in normotensive, normal-weight children/adolescents (open squares, dotted line) and adults (close lozenges, dashed line; adapted from Ref. [11]). Continuous lines are the best fitting, quadratic relation in the whole population with individual 90% confidence interval. *Panel B*: relation between stroke work and LV mass index in normotensive normal-weight (dots) and overweight-obese adults (open circles). Continuous lines are the best fitting, quadratic relation and individual 90% confidence interval in the normal-weight population shown in Panel A.

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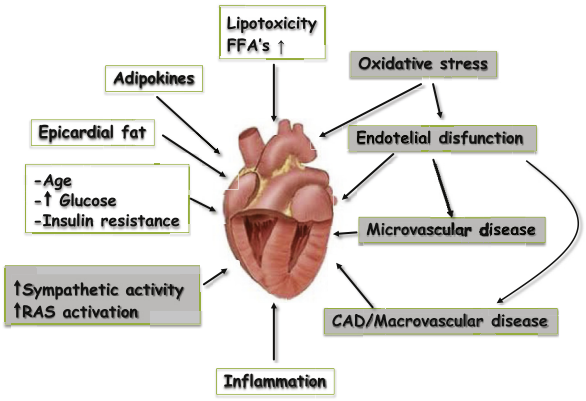

Figure 3 Non-hemodynamic determinants of LV hypertrophy in obesity. Development of LV hypertrophy is influenced by non-hemodynamic components altering structure and composition of myocardium. These include inflammatory status, increased plasma glucose and insulin resistance, increased epicardial fat, adipokines, lipotoxicity and increased levels of circulating free fatty acids (FFAs). Other mechanisms might also contribute by altering hemodynamic load (gray background), in addition to a direct cell effect (oxidative stress, endothelial disfunction, micro and macrovascular disease, sympathetic overdrive and renin angiotensin aldosterone (RAS) systems). CAD = coronary artery disease.

Study [26], a population-based study with very high prevalence of obesity, in which the variance of LV mass was explained by abdominal fat rather than insulin resistance. This finding suggests that visceral fat-related stimuli other than insulin might have more impact on LV geometric changes.

The association of increased LV mass with the obesity-related inflammatory state is particularly relevant. It has been recently suggested that LVH in obesity might be expression of the systemic inflammation, likely through contributing to the increase in tissue water content and reactive fibrosis [22].

There is evidence that structural modifications occur even in moderately obese individuals [28], attributable to increased fibrosis, an evidence already reported in necropsy studies. In addition to the increased fibrosis, there is also evidence that, accompanying the excess of abdominal fat, epicardial fat is increased in obese subjects and is related to increased LV mass [29]. In addition to the potential neuro-hormonal stimulation induced by the visceral fat surrounding epicardium, physical alterations induced by fat accumulation contribute to the structural abnormalities of myocardium [30]. Fat accumulating at the epicardial level infiltrates the myocardium [30], contributing to the obesity-related structural and functional abnormalities.

Moreover, similar to other organs, exposure of the heart to high levels of free fatty acids alters microscopic cytosolic characteristics of non-adipose tissues near to mitochondria, and impairs mitochondrial function, with structural and functional consequences also during youth [31]. Thus, the increased LV mass in obesity is the consequence of a general, inappropriate increase of all myocardial cell components and composition, yielding a global alteration of the normal structure of myocardium.

The complex of the non-hemodynamic components of the increase in myocardial mass might explain, at least in part, also the reported obesity-associated right ventricular hypertrophy, which is correlated with BMI as much as LV hypertrophy [32], and the evidence of LV mass inappropriately high for the magnitude of hemodynamic load [33,34].

The relative hemodynamic-independence of these myocardial modifications well explains the early LV geometric abnormalities detected in overweight children and adolescents, before a significant impact of blood pressure rise can be detected [11].

The pathophysiology of increase in LV mass in obesity suggests that the definition of LV hypertrophy for this increase might be misleading, as it might incorrectly address to the concept of cardiomyocyte hypertrophy, which is only one of the components of the increased myocardial mass and probably not the most important at least when pressure load is normal. When arterial hypertension develops, pressure overload is the additional stimulus that adds to the other obesity-related stimuli with an exponential effect on prevalence of LV hypertrophy [35,36] (Fig. 4). Thus, the association of obesity with hypertension combines pressure and volume overload together with a number of non-hemodynamic stimuli enhancing LV myocardial growth, with severe prognostic implications [37].

Prevalence of LV hypertrophy in obesity

Even in the absence of hypertension, obesity is frequently associated with non-optimal BP values [38], which contributes to increasing LV mass and to the prevalence of LV hypertrophy. However, assessment of LV hypertrophy in the presence of obesity is a difficult task, due to the abnormal body composition of obese subjects. To compare the level of LV mass with normal reference, normalization for body size is needed. The traditional method to normalize for body size has utilized body surface area (BSA) and, most commonly, the DuBois & DuBois formula, though it has never been validated in obesity. However, as highlighted in many articles [39—41], use of BSA as the measure of body

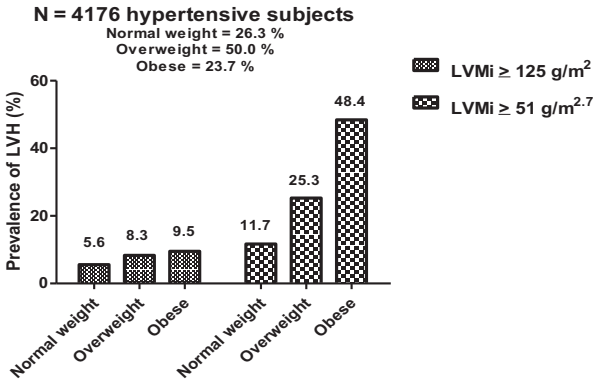

Figure 4 Prevalence of LVH in hypertensive subjects, based on normalization for BSA (dotted columns) or height$^{2.7}$ (black-squared columns). Prevalence of LVH in obese normotensive subjects is only slightly less than in normal-weight hypertensive subjects. Adapted from population in Ref. [94].

size to normalize LV mass in obesity produces an over-adjustment, due to the adipose component of the body composition, which has an impact on LV mass substantially different from lean body mass.

Based on comparative physiology studies in mammals [42,43], and on equations developed in a large normotensive and normal-weight reference population sample, encompassing the entire life-span, we proposed in 1992 to normalize LV mass for height in meters to the power of 2.7 [40]. This allometric signal appeared geometrically consistent, as relating a three-dimensional with a one-dimensional variable, which are linearly related at power of 3. Other studies have shown afterward that the allometric signal is lower than initially reported when only the adulthood is analyzed [44–46], as well as higher (i.e. 3) when only children during body growth are analyzed [47]. The apparent inconsistency is substantially due to the different age-related intra-population variability of height.

Compared to the normalization of LV mass for BSA, normalization for height in $m^{2.7}$ identifies a much greater prevalence of LV hypertrophy in obese subjects [48] (Fig. 4).

Using LV mass/height$^{2.7}$, the prevalence of LV hypertrophy ranges between 13% in obese, normotensive individuals [10] and over 75% in individuals with morbid obesity, in the presence of hypertension [35], with only a modest decrease in the hazard ratio for incident cardiovascular morbidity, compared to normalization with BSA [48,49]. As a consequence, in populations with a large prevalence of obesity, the population risk attributable to LV hypertrophy that is identified with normalization of LV mass for height$^{2.7}$ is substantially greater (17%) than with normalization for BSA (10%) or even the linear measure of height [48].

Most recently, Chirinos et al. [45] found a substantially lower allometric signal (i.e. 1.7) in the MESA, a large multiethnic population-based study, which was prognostically relevant. They also identified a strong residual negative correlation between LV mass/height$^{2.7}$ and height, which was not evident using the MESA-generated allometric signal "1.7". This residual negative relation was also confirmed in the Strong Heart Study population, but in that population, characterized by an overwhelming prevalence of obesity, the LV mass index using height$^{1.7}$ did not produce significant hazard ratio and a low population attributable risk [50]. The substantial difference between the original indication of the utility of allometric equations [40] and the lower allometric signals reported afterward [44–46] is that the first equation was obtained merging infants, children, adolescents and adults, while the subsequent analyses have been performed within adult populations (therefore with substantial less variability of height), in whom a smaller exponent reflects a substantially lower variability of the independent variable.

An interesting hypothesis, however, is that when using greater allometric signals (2.7), obtained across the entire age-span and producing the negative residual relation with height, the prognostic effect of LV mass index is also tracked by lower body height [51]. This hypothesis is based on the evidence that height seems to be a predictor of cardiovascular morbidity and mortality in a relevant number of epidemiological studies [52,53], though this evidence is contradicted by other studies [54]. A recent meta-analysis performed in a large number of studies, carefully selected, confirmed the association of low height with prognosis [54]. Whether body height tracks prognostic information obtained by LV mass index by the greatest allometric signals of height remains to be explored.

As today, the suggested partition values for LV hypertrophy in obese adults is not different from the ones suggested for the general population: 50 g/$m^{2.7}$ in men and 47 g/$m^{2.7}$ in women.

LV geometry in obesity

What is certain at this time is that using BSA to normalize LV mass in obesity may potentially lead to substantial errors. Lavie et al. [55] evaluated LV geometry in a large population sample of obese subjects with preserved ejection fraction, referred for echocardiographic exam to their institutions. Prevalence of hypertension was not reported. LV mass was normalized for BSA. The authors found a very low prevalence of clear-cut LV hypertrophy (7% for eccentric and 8% for concentric LV hypertrophy) with an overwhelming prevalence of concentric LV remodeling (34%), a geometric pattern associated with low cardiac output and high peripheral resistance [56,57]. Similar to other results obtained using BSA as the measure of body size to normalize LV mass, the Lavie's results could be substantially different with normalizations of LV mass for height$^{2.7}$, because many observations with concentric LV remodeling could shift to the concentric LV hypertrophy pattern. However, what this study highlights is the very high prevalence of concentric LV geometry (i.e. combined remodeling and hypertrophy) in obese subjects, an evidence that confirms, on a larger scale, previous and more recent findings [10,32,58] and contributes to shake the paradigm of the association of obesity with eccentric LV hypertrophy [59,60]. A strong confirmation of the association of obesity with concentric LV geometry was recently produced using magnetic resonance imaging in the MESA [61].

Mechanisms of development of concentric LV geometry in a high-output state such as obesity are unclear, but there are many potential stimuli orienting toward a concentric geometric pattern of LV adaptation in obesity [12,13].

Also the non-muscular components of the increased LV mass may thicken LV wall more than expected for the hemodynamic load. An inappropriately elevated LV mass relatively to the hemodynamic load (a condition associated with severe degrees of concentric LV geometry) has been reported in obesity [33,34]. Fat tissue infiltrating myocardium has physical characteristics different from muscular tissue, the most important of which is elasticity. Fat is a scarcely elastic tissue [62,63] and infiltration into the myocardium has to alter the tissue elastic properties, likely impairing distensibility and limiting LV dilatation. Cytosolic accumulation of fatty acid increases the size of cardiomyocytes independently of expression of sarcomeres [30,64] and, possibly, reduces cell elastance. In addition to promoting reactive fibrosis, overproduction of cytokines from the visceral adipose tissue, namely from the IL6 family, may also contribute to sarcomeric growth in both serial and parallel directions [65–67].

Moreover, in comparable conditions, in obese subjects classified as normotensive, blood pressure is almost

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invariably higher than in their normal-weight peers and predicts the incidence of overt arterial hypertension [11,38]. Hemorheologic components of total peripheral resistance influence native blood pressure [68], are associated with concentric LV geometry [69] and are altered in obesity [70]. Thus, pressure load in obese individuals is constantly higher than in normal-weight persons, even in the presence of normal blood pressure values, and might well direct the sarcomeric expression toward a parallel pattern. Yet, assessment of normal blood pressure in office, does not exclude at all the presence of daily hypertension. Masked hypertension is more frequent in obese than in normal-weight individuals [71]. Eventually, other specific conditions, associated with obesity, such as sleep apnea syndrome, contribute to explaining the prevalence of concentric LV geometry in this condition [72], by increasing the pressure overload during night.

The interesting aspect of concentric LV hypertrophy in obese individuals is the combination with a high-output state [7]. Although the increase in cardiac output is less than in obese individuals with eccentric LV hypertrophy, concentric LV hypertrophy in obesity does not follow the simple paradigm that we have proposed in 1992 [56], further elaborated later [73]. Concentric LV hypertrophy in obesity is most often associated with some degree of LV dilatation, even in the presence of normal LV chamber function, which strongly suggests a combined volume and pressure overload with particular functional consequences [74].

Sex-differences in obesity-related LV geometry

Body composition is different in women and men. In the Strong Heart Study, for each kg/m^2 of BMI, adipose tissue was substantially more abundant in women than in men [75]. Though lower than in men in absolute terms, in the Strong Heart Study, LV mass was actually greater in obese women than in obese men when normalized for height$^{2.7}$ (Fig. 5), whereas the effects of both sex and obesity were not detected when using normalization for BSA. Similarly, when LV mass was normalized for fat-free mass, obese women also exhibited greater values than men [75,76]. While BMI was not independently associated with LV mass in both genders, adipose mass and waist-to-hip ratio gave significant contribution to variability of LV mass in women but not in men, independently of the other physiological contributors (age, fat-free mass, systolic BP, hypertension and stroke volume) [75], a finding also reported in different ethnic groups [77] and in different contexts, and confirmed in a magnetic resonance study [78].

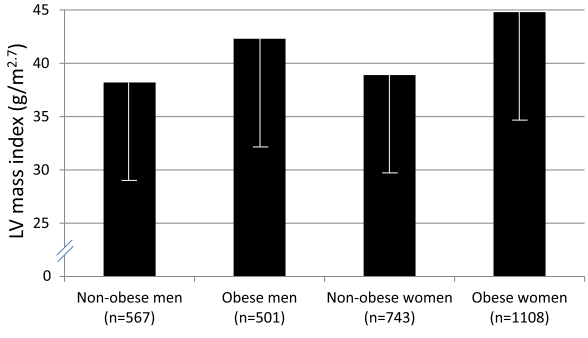

Figure 5 Mean and standard deviation of LV mass normalized by height in m$^{2.7}$ in non-obese and obese men and women, participants of the Strong Heart Study cohort. From Table 3 of Ref. [75].

Menopause does not appear to have substantial effect on the obesity-related sex-differences in LV mass [75], whereas it is one of the factors associated with the greater rate of concentric LV geometry in women [79].

Because fat-free mass is substantially less in obese women than in obese men, it would be unrealistic to interpret the increased LV mass index found in obese women as predominantly due to cardiomyocyte hypertrophy, whereas it is more likely related to non-muscular components of myocardium. As said above, central obesity is associated with activation of inflammatory markers [3,4,80] that can contribute to explaining also this gender-related differences [81]; this is consistent with the evidence that Strong Heart Study women exhibited higher levels of inflammatory markers than men. In a small series of normotensive obese women several markers of inflammation were correlated either with LV mass index and with visceral fat [66].

LV mass and weight loss

Reduction of LV hypertrophy in obese individuals is an achievable objective with significant weight loss [82,83]. This association is suggested to be even more evident than the association of decrease in LV mass with decrease in blood pressure [84]. In a large population of high-risk hypertensive patients, for comparable decrease in blood pressure, LV mass was substantially less reduced when obesity was present [85–87]. If not managed, obesity is also a strong obstacle opposing to the possibility of optimal blood pressure control by antihypertensive medications [88]. Also, in the hypertensive participants of the Strong Heart Study cohort, obesity is associated with lack of decrease, or even increase, in LV mass index over time, independently of blood pressure control and antihypertensive therapy [89].

The clear effect of weight loss on reduction of LV mass has been more recently confirmed in series of obese patients undergone bariatric surgery [90,91]. Although the reduction of LV mass observed with bariatric surgery is of similar magnitude as that obtained with sustained diet-induced weight loss [91], maintenance of a target body weight after surgery is easier than keeping patients on diet, though this advantage should be weighted by the potential complications and side-effect of surgical procedures in the long run. In contrast, aggressive antihypertensive treatment in hypertensive patients with LV hypertrophy was associated with impaired reduction in LV mass and less improvement in systolic LV function in obese compared to normal-weight subjects, despite comparable blood pressure reduction [86].

Mechanisms of improvement of LV geometry with weight loss are primarily hemodynamic, through a substantial reduction of stroke work, but also involve directly myocardial fatty acid uptake and reduction of myocardial triglyceride content [92]. These changes associated with

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weight loss might also be macroscopically observed with the substantial reduction of epicardial fat, detected by 2D echocardiography [93].

Conclusions

Obesity is a major cause of LV hypertrophy, which is sustained by the increased hemodynamic load and non-muscular components of myocardium, through mechanisms involving visceral adipose tissue. LV hypertrophy is often concentric and more pronounced in obese women than in men. Weight loss is a stimulus to reduce LV mass at least as potent as reduction in blood pressure. Given the complex mechanism involved in the development of LV hypertrophy in obesity, it could be predictable that pure interventions on hemodynamic load could not have substantial effect on reduction of LV mass [85–87]. If LV hypertrophy reduction is a target in the management of obesity, non-hemodynamic factors should have the same degree of attention as the hemodynamic load.

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Please cite this article in press as: de Simone G, et al., Left ventricular geometry in obesity: Is it what we expect?, Nutrition, Metabolism & Cardiovascular Diseases (2013), http://dx.doi.org/10.1016/j.numecd.2013.06.012

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