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Difference between Kwashiorkor and Marasmus: Comparative meta-analysis of pathogenic characteristics and implications for treatment

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1 **Abstract**

2 Kwashiorkor and marasmus are two clinical syndromes observed in severe acute
3 malnutrition. In this review, we highlighted the differences between these two syndromes by
4 reviewing the data comparing kwashiorkor and marasmus in literature, combined with recent
5 microbiological findings and meta-analysis. Depletion of antioxidants, vitamins and minerals
6 were more severe in kwashiorkor than marasmus. This was consistent with the severe and
7 uncontrolled oxidative stress associated with the depletion of gut anaerobes and the relative
8 proliferation of aerotolerant gut pathogens. This relative proliferation and invasion of gut
9 microbes belonging to the aerotolerant *Proteobacteria* phylum and pathogens suggested a
10 specific microbial process critical in the pathogenesis of kwashiorkor. Liver mitochondrial
11 and peroxisomal dysfunction could be secondary to toxic microbial compounds produced in
12 the gut such as ethanol, lipopolysaccharides and endotoxins produced by *Proteobacteria*,
13 particularly *Klebsiella pneumoniae*, and aflatoxin produced by *Aspergillus* species. The gut-
14 liver axis alteration is characterised by oedema and a fatty and enlarged liver and was
15 associated with a dramatic depletion of methionine and glutathione, an excessive level of free
16 circulating iron and frequent lethal bacteraemia by enteric pathogens. This was consistent
17 with the fact that antibiotics improved survival only in children with kwashiorkor but not
18 marasmus. The specific pathogenic characteristics of kwashiorkor identified in this review
19 open new avenues to develop more targeted and effective treatments for both marasmus
20 and/or kwashiorkor. Urgent correction of plasma glutathione depletion, alongside supply of
21 specific essential amino acids, particularly methionine and cysteine, early detection of
22 pathogens and an antibiotic more efficient than amoxicillin in suppressing gut *Proteobacteria*
23 including *K. pneumoniae*, and probiotics to restore the human gut anaerobic mature
24 microbiota could save many more children with kwashiorkor.

25 **Keywords:** severe acute malnutrition, marasmus, kwashiorkor, children, protein,
26 antioxidants, microbiome

27 **1. Historical perspective and current status of knowledge**

28 Marasmus has been described for the longest as the typical form of severe
29 malnutrition; it was referred to as phthisis, dystrophy and cachexia. Oedematous malnutrition
30 was first described in Latin America during the 19th century in several unobtainable
31 publications cited by Autret and Béhar (1). The first publication to include typical pictures
32 was from the French literature in 1913 by Guillon, where the syndrome was called
33 "Bouffissure d'Annam" or swelling disease of Vietnam (2). Twenty years later, Dr. Cicely
34 Williams, in her work in the colonial Ghana described this disorder as "a nutritional disease
35 of childhood associated with a maize diet" and named the condition "Kwashiorkor" (3,4).

36 At the first session of the Joint Food and Agriculture Organization (FAO)/World
37 Health Organization (WHO) Expert Committee on Nutrition in 1949, kwashiorkor was
38 considered to be of widespread concern in developing countries and investigation was
39 recommended (5). Thus, during the early 1950s, Brock and Autret carried out a survey in
40 Africa. They reported that cases of kwashiorkor occurred in the twelve nations visited
41 (belonging to all regions of sub-Saharan Africa namely central, west, east and southern
42 Africa) and provided a clear description of its major signs and symptoms (6). The main
43 conclusion was that kwashiorkor appeared to be related to a low protein diet, usually in
44 weaning infants with clinical features including oedema, skin and hair dyspigmentation and
45 fatty infiltration in liver, confirming the description of Dr. Williams in 1933 (3). The report
46 by Brock and Autret was followed by a similar WHO/FAO study by Waterlow and Vergara
47 on kwashiorkor in Brazil (7). They mentioned in their report that cases of "Síndrome
48 Policarencial Infantil" (the name of kwashiorkor in Brazil) was found as an apparently
49 identical form to the African syndrome. However, several cases were assessed as
50 intermediate stages with less defined characteristics and variable manifestations such as

51 “wasting and oedema but normal liver” or “stunting and hair dyspigmentation but no
52 oedema” (7).

53 This suggested coexistence between kwashiorkor and marasmus. Indeed, previously
54 in 1953, the third session of the joint FAO/WHO Expert Committee on Nutrition (8)
55 recognized the possible existence of intermediate cases between kwashiorkor and marasmus.
56 According to this Committee, marasmus, which was called “severe undernutrition”, related to
57 a prolonged insufficient diet with reduced carbohydrates and fat (besides protein deprivation)
58 and was distinct from kwashiorkor which was “protein malnutrition” due solely to an
59 inadequate protein intake (8). After stating that the problem of definition was “without
60 descriptive significance”, the Committee then highlighted the need to determinate a proper
61 terminology in defining the diagnostic characteristics of kwashiorkor and marasmus; as well
62 as the importance of a detailed description and an administrative practice guideline to
63 ultimately solve this problem (8). During the same year, at the 3rd session of the Joint
64 FAO/WHO Expert Committee, a conference about protein malnutrition was held in Jamaica;
65 they considered how to give accurate descriptions of the conditions, the classification for
66 kwashiorkor, and the definition of the terms “kwashiorkor”, “marasmus” and “marasmic-
67 kwashiorkor” (9). The conference could not reach a consensus (9).

68 In 1959, Rao conducted his survey on protein malnutrition in 10 areas in Southern
69 India and observed that the prevalence of kwashiorkor represented only 1% among children,
70 but marasmus was observed in nearly twice as many children as kwashiorkor – 1.7% vs 1%
71 (10). He stated that it was not “uncommon” to find intermediate types in one child which
72 were frequently related to diets deficient in both calories and protein (10). In the early 1960s,
73 the 6th session of the Joint FAO/WHO Expert Committee considered the importance of
74 marasmus and confirmed that all aspects of the problem of protein-calorie-deficiency disease
75 should be assessed “without decreasing the interest in kwashiorkor” (11). The Committee

76 also proposed a classification of nutritional diseases based on the nutrient deficiencies and
77 clinical signs (11). Accordingly, kwashiorkor and marasmus were two main categories of a
78 “new” condition termed “protein-calorie” malnutrition. In 1966, McLaren stated that the
79 distinction between kwashiorkor and marasmus was important (12). Especially, he mentioned
80 that kwashiorkor tended to occur in children aged 1-4 years of age whereas marasmus
81 occurred most frequently in those under 1 year of age (12) and thereby, the focus should be
82 placed on the younger age group.

83 In 1970, the Wellcome Trust sponsored a meeting to try to resolve the question of
84 definition. It was agreed that the term kwashiorkor should be confined to those children with
85 oedema and marasmus to those with a low weight for age; marasmic-kwashiorkor was used
86 for children with a low weight-for-age and oedema. Hair, skin and liver signs were not used
87 in the definitions (13). It was refined by Waterlow in 1972 by replacing weight-for-age with
88 weight-for-height (14) as low weight-for-age included children who were stunted as well as
89 emaciated (15). These definitions have been generally accepted and are those currently
90 recommended by WHO using their latest anthropometric standards. Some countries, such as
91 India and Mexico have used different classifications, and the severity of marasmic cases has
92 changed as new anthropometric standards have been introduced. In some publications,
93 kwashiorkor and marasmic-kwashiorkor have been combined and are then termed
94 “oedematous malnutrition”.

95 However, even though many studies had focused on these definitions, in practice
96 there is often a marked overlap between the other symptoms and signs common in severely
97 malnourished children. This makes our understanding of the pathophysiology and aetiology
98 of these two forms of severe malnutrition incomplete. In this review, we attempted to point
99 out the potential specific features of kwashiorkor and marasmus by reviewing the data
100 comparing kwashiorkor and marasmus. It should be emphasised, however, that the two types

101 of cases reported in the literature are normally differentiated on the basis of oedema and
102 anthropometry solely; none of the studies have further classified the patients into those with
103 or without hair, skin or hepatic abnormalities, accompanying stunting or other clinical
104 features (except over infection in some reports).

105 **2. Methods**

106 In this review, we searched papers from PubMed and Google Scholar in accordance
107 with the PRISMA statement (**Checklist S1**). The search terms were used are kwashiorkor OR
108 “protein malnutrition” OR “oedematous malnutrition” OR “marasmus” OR “non-oedematous
109 malnutrition”. We reviewed all observational studies including cohort studies, case-control
110 studies, randomized control trials, cases report with at least one case of kwashiorkor and one
111 case of marasmus as well as studies comparing kwashiorkor and marasmus until the last
112 searched date on October 31st, 2019. In addition, since the late 1940s, three United Nations
113 (UN) agencies - FAO, WHO, and United Nations Children's Fund (UNICEF) with their
114 expert committees substantially contributed to the evolution of nutritional science and
115 addressed nutritional deficiencies in developing countries. Thus, reports from FAO, WHO
116 and UNICEF official websites were collected as a support source. We selected the Joint
117 FAO/WHO Expert Committee on Nutrition as well as reports from authors who worked for
118 FAO and WHO such as Autret, Béhar, Waterlow and those at INCAP (Institute of Nutrition
119 of Central America and Panama), particularly Scrimshaw.

120 Next, random-effects meta-analysis was performed using Revman 5.3 software (16),
121 using a different weighting scheme that depends on the risk difference measure for
122 dichotomous outcomes and on the mean difference measure for continuous outcomes. Here,
123 we defined 4 grades of quality of evidence for each characteristic analysed by meta-analysis
124 to examine items that were potentially specific for one or other of the two conditions (**Table**
125 **1**). Grade A included characteristics which were assessed in at least 2 studies with more than

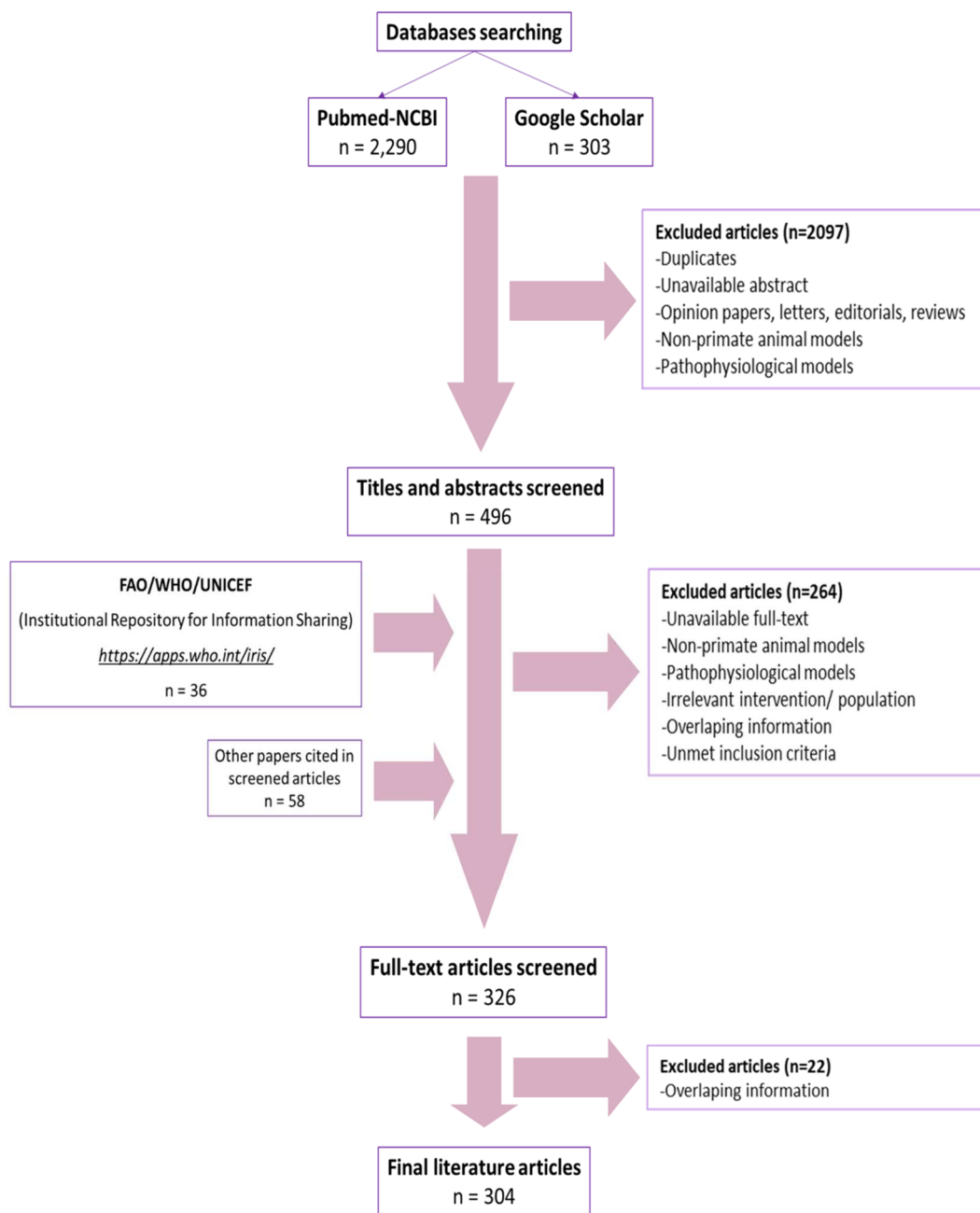
126 80% results with a consistent direction of effect (decreased/increased in
127 kwashiorkor/marasmus) and a significant summary effect ($p < 0.05$). Grade B was composed
128 of characteristics which were also assessed in at least 2 studies with more than 80%
129 consistent results, but the meta-analysis results didn't reach significance. Grade C listed the
130 characteristics of which the data were available only in one study and the results were
131 reported to be significant. Last, characteristics assessed in at least 2 studies with less than
132 80% consistent results were all classified in Grade D. Particularly, Grades A, B and C were
133 divided into 2 sub-groups: specific characteristics (which occurred only in kwashiorkor or
134 marasmus) and non-specific characteristics (which occurred in both kwashiorkor and
135 marasmus but were more pronounced in one form compared to the other). All data collected
136 are listed in **Suppl. Table S1** and summed with meta-analysis classification in **Table 1** (for
137 specific characteristics) and **Suppl. Table S2** (for non-specific characteristics).

138 For quantitative analysis, the risk of bias assessment in each included study was performed
139 following the Cochrane risk-of-bias assessment tool. Consequently, we classified each
140 included study as 'low risk', as 'high risk, or as 'unclear risk', with the last category
141 indicating lack of information. Risk of bias domains for intervention trials were random-
142 sequence generation (selection bias), allocation concealment (selection bias), blinding of
143 participants and personnel (performance bias), blinding of outcome assessment (detection
144 bias), incomplete outcome data (attrition bias), selective outcomes reporting (reporting bias),
145 and other potential sources of bias (**Suppl. Figure S1**). All figures were generated using
146 RevMan 5.3 software.

147 **3. Results**

148 Over 2,200 articles were collected, of which ~600 articles met the inclusion criteria for full
149 text review articles, 36 articles added from FAO/WHO/UNICEF, 58 articles cited in the
150 screened articles. Finally, 304 articles were included in this review including 88 for
151 quantitative analysis after excluding duplicates, articles reporting overlapping information or
152 irrelevant studies such as non-primate animal models and physiopathological models (**Figure**
153 **1**). Risk of bias of each study were presented in **Suppl. Figure S1-S2** and **Suppl. Table S3**.

154 **Figure 1: Flow-chart showing the results of literature research**



156 **3.1 Difference in Epidemiology**

157 - Incidence and Prevalence:

158 Kwashiorkor was often the predominant form of protein-energy malnutrition admitted
159 to hospitals in Uganda, Zambia, Nigeria and Columbia (**Figure 2, Suppl. Table S4**). In
160 contrast, marasmus appeared to be the predominant form of severe malnutrition with
161 kwashiorkor representing only a minority of the total admissions in Sudan, Ethiopia,
162 Bangladesh, Burkina Faso and Cameroon (**Figure 2, Suppl. Table S4**). Similarly,
163 community surveys show a much lower relative prevalence for kwashiorkor than marasmus.
164 Rao reported from Southern India that the prevalence of marasmus was twice that of
165 kwashiorkor (10) and Broeck (Democratic Republic of Congo) gave the median prevalence
166 over all survey rounds of 3.2% for marasmus but only 0.2% for kwashiorkor (17). During the
167 early 1970s, a study by Bengoa showed the prevalence in developing countries was 0.2%-
168 1.6% for kwashiorkor and 1.2%-6.8% for marasmus. It is noteworthy that the hospital
169 admissions will be closer to the incidence rate whereas the survey data of Rao, Broeck and
170 Bengoa give prevalence.

171 **Figure 2: Incidence of Kwashiorkor and Marasmus in studies regarding malnourished**
 172 **children admitted to hospital**



187 * Colour intensity was determined by frequencies of Kwashiorkor, Marasmus and Marasmic-
 188 kwashiorkor. Accordingly, higher frequencies corresponded to stronger colour.

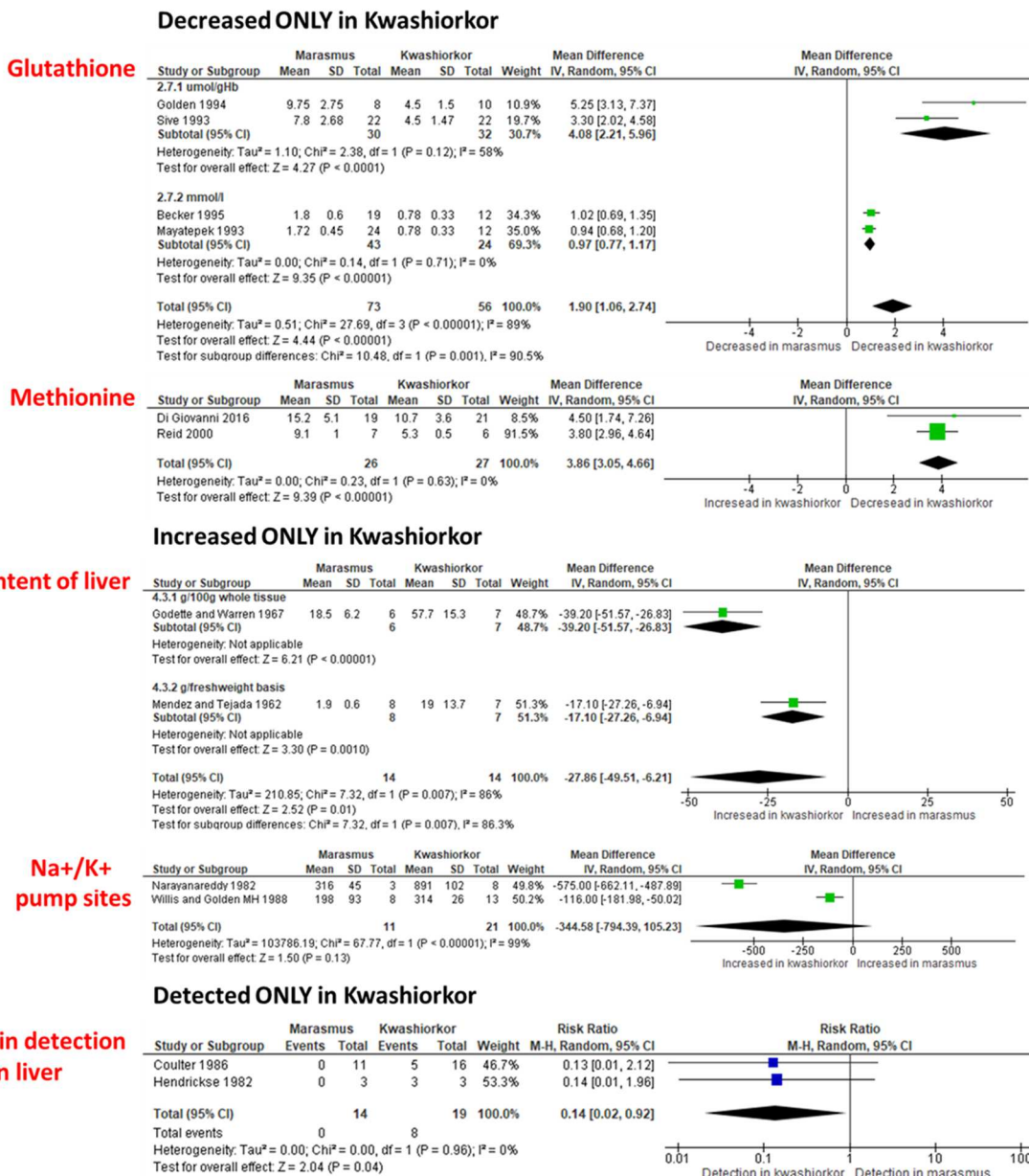
189 As noted by Gopalan (18) and Fitzpatrick (19), some communities consistently
190 generate many more cases of kwashiorkor while other nearby communities sharing the same
191 general environment and services do not. They suggested that there were factors that could
192 increase the risk of kwashiorkor or other factors could be protective against kwashiorkor
193 determined geographically. Indeed, later in 1973, Annegers (20,21) conducted a clinical
194 survey and concluded that “frank” kwashiorkor frequently occurred in the zone of low dietary
195 protein-calorie ratios while marasmic children were observed throughout West Africa
196 “regardless of protein levels”. Indeed, Raoult’s surveys (22) in various countries of West
197 Africa showed that kwashiorkor was most common where the diets were dominated by “root
198 and tuber” or “maize or rice as the staple” such as in the Ivory Coast but kwashiorkor was
199 rare or mild in the Sudan.

200 In addition, kwashiorkor tended to be more common in the rainy season (23,24).
201 Lindtjørn reported that marasmus was the most common form of acute malnutrition in most
202 areas of Ethiopia, whereas two areas, Kambata-Hadiya and Wolayta (known to have humid
203 and temperate climate), had a high kwashiorkor prevalence rate (24). Aflatoxins (produced by
204 *Aspergillus spp.*), which are particularly prevalent in areas of high relative humidity (25),
205 were consistently detected in the liver and increased in the plasma of children with
206 kwashiorkor (**Grade A - Figure 3-4**). However, the difference in damage caused by aflatoxin
207 in kwashiorkor and marasmus is likely to be related to the glutathione depletion in
208 kwashiorkor (26). Conversely, there are areas where aflatoxin is not found in children with
209 kwashiorkor (27).

210 Overall, diets, geographical locations, climate and aflatoxin exposure appeared to be
211 key factors affection the ratio between the prevalence of kwashiorkor and marasmus.

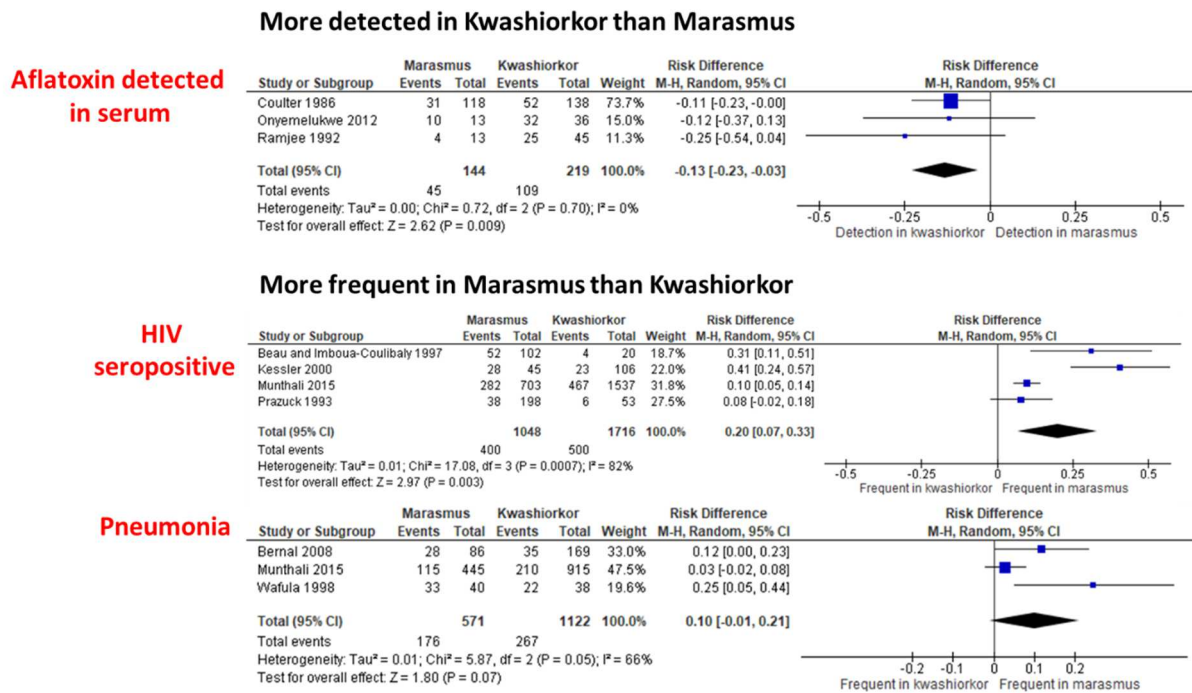
212 **Figure 3: Specific characteristics in Kwashiorkor (Grade A and B)**

213



214 **Figure 4: Difference in co-morbidity confirmed by meta-analysis between Kwashiorkor**
 215 **and Marasmus (Grade A and B, non-specific)**

216



217 - Mortality:

218 In 1958, Béhar's findings demonstrated that kwashiorkor was a significant cause of
219 death in 4 highland villages of Guatemala with a mortality rate of 20 per 1000 individuals and
220 58% of cases occurred in children under the five years of ages (28). Indeed, most studies
221 reported that mortality occurred more frequently in oedematous malnutrition than in non-
222 oedematous malnutrition, regardless of a geographic factor (**Table 2**). The mortality from
223 severe malnutrition was up to 40% for many years (29); this has been ascribed to an incorrect
224 understanding of the pathophysiology and consequent incorrect treatment. It has recently
225 fallen to lower levels, with kwashiorkor having about twice the mortality of marasmus;
226 children with both conditions have a very high mortality rate (30).

227 - Co-morbidity and Infection:

228 WHO experts confirmed that severe malnutrition generally had a synergistic
229 interaction with infection (31). Infections are very common in malnourished children; the
230 most common were gastro-enteritis, septicaemia, bronchopneumonia, tuberculosis and
231 intestinal parasites. In 1958, Béhar through his investigation into the causes of death of
232 children in 4 rural communities in Guatemala demonstrated the correlations between
233 malnutrition, diarrhoea and other infectious diseases: diarrhoea was presented in 98% of the
234 cases and bronchopneumonia in 70% of the cases (28). He suggested that infection initiated
235 and precipitated the stress that leads to the development of kwashiorkor in many cases. One
236 year later, Scrimshaw noted that kwashiorkor often occurred in children just after an acute
237 infection, most commonly diarrhoea or measles (32,33). This did not apply to all infections;
238 they showed that intestinal parasites which were usually considered as an additional stress
239 factor in the pathogenesis of kwashiorkor, were as common in children of the same age
240 without kwashiorkor as in those with kwashiorkor (32,33). Through the 1960s and 1970s,
241 from a study in Santa Maria de Cauqué (a Guatemalan village), Mata determined that

242 gastrointestinal infection was a major factor that damaged intestinal mucosa thus causing
243 malabsorption; he concluded that infection played a major part in the development of
244 malnutrition (34). Marasmus was the predominant form of malnutrition amongst HIV
245 infected children; it was consistently reported in many studies and confirmed by our meta-
246 analysis (**Grade A- Figure 4**). Bacteraemia (**Grade C**) was reported to be 3.5 times more
247 common in kwashiorkor than marasmus in a hospital study by Friedland in South Africa most
248 frequently due to gram-negative enteric microorganisms (35). The proportion of deaths due to
249 bacteraemia was much higher in kwashiorkor than marasmus, 25% and 2%, respectively (35).
250 Meanwhile overall mortality rate in the 2 groups was similar, 13% for kwashiorkor and 15%
251 for marasmus (35).

252 These results show a marked difference between marasmus and kwashiorkor and also
253 show a good correlation of the 2 diseases with their clinical characteristics. Marasmus is a
254 more chronic illness, characteristics of a deprivation syndrome and appears to be the most
255 prevalent type of severe acute malnutrition (SAM) in many regions and is most frequent in
256 those with HIV infection. Kwashiorkor in typical cases is an acute disease which is usually
257 precipitated by infection (diarrhoea, measles) and complicated by septicaemia and frequently
258 fatal bacteraemia.

259 **3.2. Difference in Nutrition**

260 The prevailing concept of the aetiology of marasmus and kwashiorkor from the onset
261 of the investigation by the United Nations was that marasmus resulted from a lack of energy
262 from foodstuffs, severe long-term food deprivation or very early weaning, whereas
263 kwashiorkor was associated with improper weaning and a diet deficient in protein. These
264 views were officially endorsed in the 3rd report of FAO and WHO (8) which stated that
265 marasmus occurs after prolonged carbohydrate and fat deprivation (in addition to protein
266 deprivation) whereas kwashiorkor is characterized by inadequate protein intake. Then, in

267 1962, the 6th report of FAO/WHO (11) designated kwashiorkor and marasmus and
268 intermediate stages (marasmic-kwashiorkor) as "protein-calorie deficiency diseases". From
269 that moment on, kwashiorkor was defined as one form of severe malnutrition which is related
270 diet with severe deficiency in protein (or good-quality protein) relative to energy. In contrast,
271 marasmus is related to a balanced deficiency of protein and calories or inadequate amounts of
272 good-quality diet (36). This was first challenged by Gopalan when he looked at the diets of
273 children with kwashiorkor and marasmus in India and found no qualitative or quantitative
274 differences in the diets of the two groups of children, suggesting an additional non-dietary
275 factor at play in kwashiorkor (18).

276 More recently, this early observation has been confirmed in terms of protein and
277 energy, however differences were found. Sullivan in 2006 reported that eggs and tomatoes
278 (important source of antioxidant micronutrients, including vitamin C, lycopene and
279 carotenoids) were consumed less frequently by children with kwashiorkor than those with
280 marasmus (37). Next, Kismul in 2014 showed that children with kwashiorkor consume fewer
281 sweet potatoes and papaya which are characterized by a high β -carotene content (38). The
282 reports of Sullivan and Kismul stressed the importance of antioxidant foods and suggested a
283 possible aetiological association between antioxidant consumption and kwashiorkor. Thus,
284 empirical dietary evidence that children with kwashiorkor have a specific decrease in total
285 protein intake as the basis of their illness has not been confirmed.

286 Since the Biafran war, milk has been the mainstay of the nutritional treatment of
287 malnutrition. A study by Brewster showed that, despite the similar densities in protein and
288 energy, maize based diets were inferior to milk. Maize based diets appeared to be associated
289 with a defect of intestinal mucosal barrier function whereas one of the beneficial effects of
290 milk was an improvement of intestinal permeability (39). Kwashiorkor children had a lower
291 mortality with the milk-based diet compared with a maize-based diet (39). Despite the

292 evidence that milk-based diets had been used successfully for rehabilitation for many years,
293 there was a political problem due to consideration that lactose intolerance and cows' milk
294 allergy might affect the treatment of predominantly black children in the developing world.
295 This was based upon a consideration in the USA that black children were intolerant to milk
296 whereas white children are tolerant; consequently, this led to cow's milk allergen avoidance
297 and replacement by a nutritionally deficient diets (such as Rice Dream milk™, goat's milk,
298 sugared soft drink) (40-42). Due to this consideration, some kwashiorkor cases were reported
299 in rich developed countries as a consequence of unorthodox diets and nutritional ignorance of
300 well-intending but misinformed parents; examples are unnecessarily restrictive diets based on
301 a principle of exclusion during illness like the "fruitarian" diet (4,43,44). As a consequence,
302 some restrictive diets are leading increasingly iatrogenic nutritional issues. Indeed, both
303 marasmus and kwashiorkor have been mentioned in several reports as the results of medical
304 mismanagement leading to negligent adverse events (45,46). These reports emphasized the
305 potential danger of inappropriate restrictive diets in infants and stressed the need for careful
306 nutritional guidance in the management of nutritional diseases (42).

307 Overall, the only difference in dietary nutrient intake between kwashiorkor and
308 marasmus confirmed with reliable data is the inadequate high-antioxidant food consumption
309 by kwashiorkor patients; this taken together with the change in plasma antioxidant levels
310 (which we will discuss later in "Difference in Biologic features") appear to be a potential
311 discriminant characteristic of kwashiorkor from marasmus.

312 **3.3. Difference in Clinical features**

313 In 1933, Dr. Williams described kwashiorkor as a well-marked syndrome with the
314 presence of oedema, particularly of the hands and feet, followed by wasting, diarrhoea,
315 irritability, frequent inflammation of the mucous membranes, variable skin dyspigmentation
316 with skin peeling; these features were described as "constant and unique" (3). The syndrome

317 occurred in children of either sex, between one and four years old. A “pale, fatty and almost
318 diffluent” liver was found as a special characteristic in children post-mortem (3). Later,
319 Brock and Autret (6) described in detail the clinical features in children with kwashiorkor in
320 West Africa. In their report, they listed 10 clinical characteristics commonly observed in
321 kwashiorkor. The stunting, gastro-intestinal disorders (diarrhoea) and anaemia were common
322 to both kwashiorkor and marasmus. Compared to marasmus, which was characterized by a
323 loss of subcutaneous fat, extreme muscle wasting and atrophy of most organs (47),
324 kwashiorkor differed in the unique features of massive oedema and the specific changes of
325 hair, skin and liver (**Figure 5-6**). The basic skin changes in kwashiorkor were
326 dyspigmentation, with "enamel paint", "flaky paint" or "crazy paving" dermatosis. In
327 contrast, none of the skin changes associated with kwashiorkor is observed in the “typical”
328 infant with marasmus whose skin is dry, wrinkled, and loose, due to marked loss of
329 subcutaneous fat. In marasmus, although the liver and other essential organs are much
330 reduced in size, histological changes are minimal (47), unlike kwashiorkor which is typically
331 characterized by a large fatty liver, fibrosis and dysfunction of several organs (such as
332 pancreatic, renal and mental functions). The mean age at presentation of kwashiorkor
333 children tended to be higher than for marasmus. Kwashiorkor was more associated with
334 bacterial infection, especially bacteraemia and septicaemia whereas marasmus is more
335 associated with HIV infection and rickets. Other signs and symptoms typical of specific
336 vitamin-deficiency syndromes might be found, or not, with a wide variation in clinical
337 characteristics in both kwashiorkor and marasmus.

338 Following the work of Brock and Autret, Waterlow and Vergara (7) reported their
339 findings of kwashiorkor in Brazil and reported intermediate cases (marasmic-kwashiorkor).
340 As stated by Gopalan in 1968 (18), children with marasmus might develop kwashiorkor and
341 children with kwashiorkor might present the picture of marasmus after shedding their

342 oedema. Clinically, most of the changes in kwashiorkor and marasmus might be present in
343 the mixed form. It has gradually become clear that kwashiorkor and marasmus are different
344 but related and possibly overlapping diseases, with marked differences in their clinical
345 features (**Figure 5-6**).

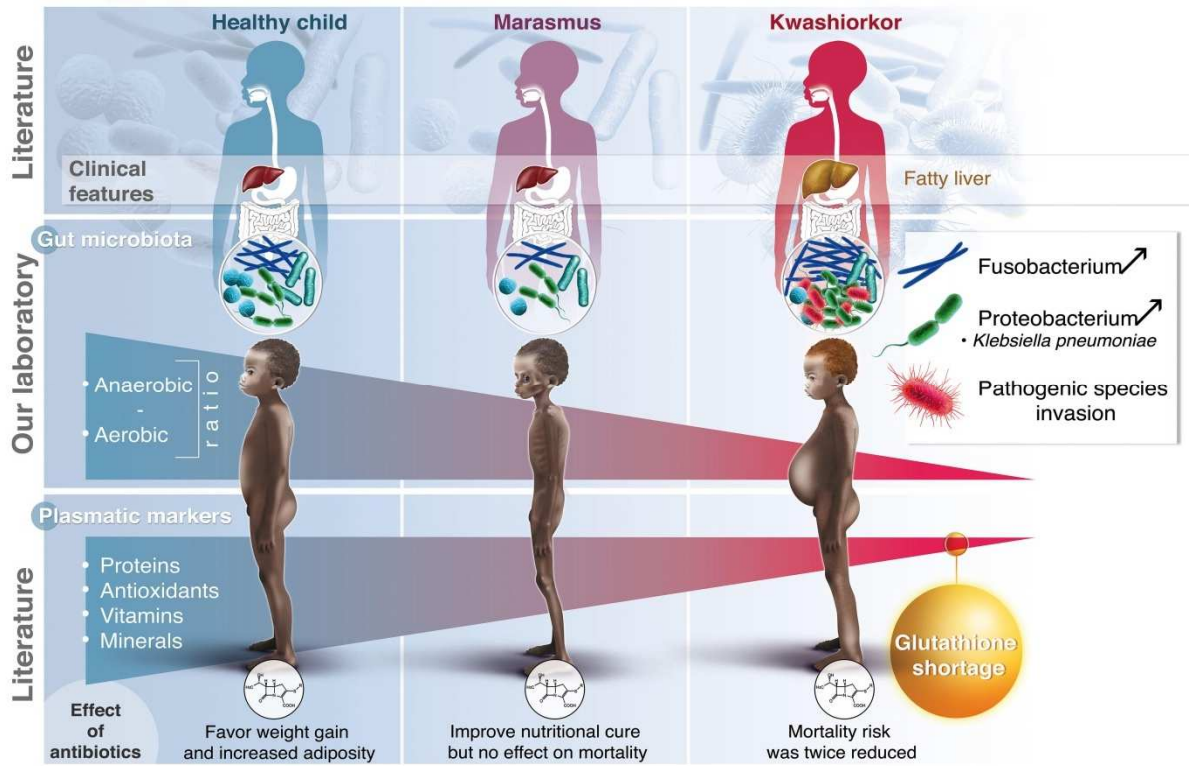
346 **Figure 5: Difference in clinical features between children suffering from Kwashiorkor**
347 **(left) and children suffering from Marasmus (right)**

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360 Illustrations represent the typical features of most cases of Kwashiorkor and Marasmus:
361 bilateral oedema and depigmented hair in Kwashiorkor; loss of subcutaneous fat and muscle
362 mass in Marasmus. Copyright 2019 by Michael Golden, written consent obtained.

363 **Figure 6: Differential characteristics in Kwashiorkor and Marasmus**



364

365

366 **3.4. Difference in Biological features**

367 - Free radicals and Antioxidants:

368 One of the earliest studies on the role of free radicals and antioxidants in malnutrition
369 pathogenicity was the study of Golden and Ramdath (48). In the study, they reported that
370 ferritin, a storage form of iron, was particularly high in kwashiorkor whereas the plasmatic
371 vitamin E and zinc concentrations were at a low level; there were especially low levels of
372 antioxidant enzymes such as glutathione peroxidase and very low levels of erythrocyte
373 glutathione (48). The findings effectively initiated the hypothesis that kwashiorkor results
374 from an excess of free radicals and a depletion of antioxidants which opened a new era for
375 malnutrition science. Indeed, several studies have been conducted since, and have confirmed
376 the low level of glutathione observed only in kwashiorkor but not marasmus (**Grade A -**
377 **Figure 3, Table 1**). Furthermore, the decrease in plasma levels of antioxidant proteins
378 (mainly albumin, transferrin and ceruloplasmin), minerals (zinc, copper, selenium) and
379 vitamins (such as vitamin A, C) consistently showed a downward trend from healthy children
380 to marasmus with the lowest levels always observed in kwashiorkor (**Suppl. Table S1-S2**)
381 which was significantly confirmed by our meta-analysis (**Grade A (Grade B for Vitamin C)**
382 **- Figure 7, Suppl. Figure S3**). Importantly, these were associated with a low
383 NADPH/NADP ratio, indicating a change in cellular redox potential towards an oxidation
384 of the cellular environment (49).

385 **Figure 7: Non-specific characteristics differentiating Kwashiorkor from Marasmus**

		Decreased in marasmus	Decreased in kwashiorkor
387	1. Plasma total protein, albumin, transferrin	Grade A	✓
388	2. Minerals (Zinc, Copper, Selenium)	Grade A	✓
389	3. Vitamin A	Grade A	✓
	4. Vitamin C	Grade B	✓
390	5. Plasma phosphate	Grade A	✓
	6. Amylase	Grade A	✓
391	7. Cholesterol, Phospholipids	Grade A	✓
392	8. Free Fatty Acids	Grade B	✓
	9. Insulin, T3 hormone	Grade A	✓
393	10. T cells count, C3 component, IgA	Grade A	✓
394	11. IGF-1, Leptin	Grade A	✓
		Increased in marasmus	Increased in kwashiorkor
396	1. ALT/AST	Grade A	✓
397	2. Growth hormone	Grade A	✓
398			

399 Non-specific characteristics were observed in both kwashiorkor and marasmus but
 400 always more pronounced in kwashiorkor (**left**) or marasmus (**right**). Consequently, all non-
 401 specific characteristics in Grade A and B (meta-analysis results $p < 0.10$ only) were summed
 402 up.

403 On another hand, a high concentration of free circulating iron in children with
404 kwashiorkor has been clearly demonstrated (50) which was not observed in marasmus
405 (51,52). Specifically, a very high level of circulating ferritin observed in kwashiorkor but
406 normal or slightly raised in marasmus (49, 53, 54). The presence of free iron in kwashiorkor
407 was confirmed through iron excretion following deferoxamine administration (55) and
408 measurement of liver iron from kwashiorkor children at autopsy (56,57). These results
409 confirmed that children with kwashiorkor were suffering from significant iron overload
410 which did not occur in marasmus.

411 - Protein and Amino acids metabolism:

412 Several studies consistently reported that the depletion in plasma total protein,
413 albumin and transferrin was more pronounced in kwashiorkor than in marasmus; this was
414 confirmed by our meta-analysis (**Grade A - Figure 7, Suppl. Figure S3A**).

415 In 1998, Manary demonstrated that the rates of whole-body protein breakdown and
416 protein synthesis are slower in children with kwashiorkor than in those with marasmus during
417 acute infection (58). Then, in 2005, Jahoor confirmed this difference and indicated the
418 different responses in protein metabolism to food deprivation between children with and
419 without oedematous malnutrition (59) which suggested that only children with marasmus had
420 the ability to maintain body protein breakdown at the same rate as well-nourished while
421 children with kwashiorkor did not have this capacity.

422 It was demonstrated that kwashiorkor children have a high disturbance of amino acid
423 metabolism with a consistent and significant reduction of plasma essential amino acids levels
424 with individual amino acids affected to different degrees (60-64). Some non-essential amino
425 acids remained at average levels (62) or might be kept at high level in the plasma of these
426 children (61,63,64). In contrast, there was a particularly marked reduction of cysteine in
427 erythrocytes and methionine in plasma (**Grade A - Figure 3**) and the flux of these amino

428 acids during whole body protein turnover was compromised. According to Jahoor, in the
429 oedematous children, the low levels of these 2 major sulphur-containing amino acids was
430 associated with slower glutathione synthesis (65). Since there was no difference in the
431 experimental diets given to the oedematous and non-oedematous children, Jahoor stated that
432 the severe shortage of methionine in oedematous children might be the result of a slower rate
433 of whole-body protein breakdown in oedematous children rather than a dietary deficiency
434 (65). Also, in his report, cysteine released from protein breakdown was slower in the
435 oedematous group; however, the amount of cysteine in non-oedematous children was still
436 sufficient to maintain its concentration in plasma and erythrocytes as well as glutathione
437 synthesis rate; this explained why during acute infection oedematous children were unable to
438 maintain glutathione synthesis rate, but non-oedematous children could (65).

439 - Lipid metabolism:

440 Increased plasma concentrations of free fatty acids (FFA) were often found in both
441 kwashiorkor and marasmus although the values were consistently higher in kwashiorkor than
442 in marasmic children (**Grade B - Figure 7, Suppl. Figure S3B**). In almost all reports, plasma
443 total cholesterol and phospholipids were consistently and significantly lower in kwashiorkor
444 than marasmus (**Grade A - Figure 7, Suppl. Figure S3B**). Plasma fasting triglycerides are
445 usually low in kwashiorkor (66,67) but not consistently; similarly, cholesterol and
446 phospholipids levels are low, while in marasmus, triglycerides are normal or increased
447 (68,69).

448 Compared to marasmus, the fatty liver is more intense in kwashiorkor. The high fat
449 content in liver was consistently and significantly reported in kwashiorkor in several studies
450 (**Figure 3, Table 3**). However, the high free fatty acid levels alone couldn't fully explain the
451 fatty liver in kwashiorkor. Lewis suggested that in marasmus, the liver responded to an
452 excessive input of fatty acids by increased production of plasma lipoproteins, whereas in

453 kwashiorkor the liver was unable to dispose of fatty acids which led to lipid accumulation in
454 the liver (67). This has been associated with mitochondrial and peroxisomal dysfunction and
455 to the lack of peroxisomes that are seen on electron microscopy of kwashiorkor livers (70,71)
456 and confirmed experimentally (72). It is of interest that the liver fat is very slowly mobilised
457 during recovery despite the fact that treatment consists of a very high fat diet (73).

458 It has been hypothesized that one factor associated with poor prognosis in
459 kwashiorkor, but not in marasmus, is impaired lipid catabolism, which limits the supply of
460 energy that is essential for survival when dietary intake is inadequate. In keeping with the
461 hepatic studies, Badaloo suggested inefficient mobilization and utilization of lipid for energy
462 in kwashiorkor but not in marasmus was due to a less efficient fat break down and fatty acids
463 oxidation in kwashiorkor using stable isotope tracer dynamic studies (74). It has been
464 demonstrated that the level of plasma carnitine was significantly lower in children with
465 kwashiorkor (61,75). Thereby, decreased fatty acid transported by carnitine across the inner
466 mitochondrial membrane for β -oxidation could be another factor contributing to slower lipid
467 oxidation in children with kwashiorkor (74).

468 - Endocrine changes:

469 In general, fasting glucose is in the low-normal range accompanied by a low fasting
470 serum insulin level; this occurs in both kwashiorkor and marasmus without a clear difference
471 between the groups (**Grade A - Figure 7, Suppl. Figure S3E, Suppl. Table S1-S2**). Becker
472 showed an impaired insulin response in most children with kwashiorkor and some children
473 with marasmus (76) and suggested that impairment in glucose tolerance in kwashiorkor might
474 be related to disturbed insulin secretion. Indeed, endogenous glucose production (EGP)
475 which is an important determinant of glucose tolerance, was demonstrated to be decreased in
476 kwashiorkor compared with marasmus (**Grade A - Figure 7, Suppl. Figure S3E, Suppl.**
477 **Table S1-S2**).

478 Growth hormone was inconsistently raised in both kwashiorkor and marasmus; but in
479 most studies, the mean values were significantly higher in kwashiorkor than in marasmus
480 (**Grade A - Figure 7, Suppl. Table S1-S2, Suppl. Figure S3E**). The loss of adipose tissue
481 was found to be more prominent in marasmus compared with kwashiorkor, and this is
482 consistent with reduced levels of leptin and IGF-1 (insulin-like growth factor-1) (**Grade A -**
483 **Figure 7, Suppl. Table S1-S2, Suppl. Figure S3E**).

484 Furthermore, thyroid hormones T3 and T4 levels were consistently lower and TSH
485 levels were higher in kwashiorkor compared to marasmus (**Grade A, B and B, respectively -**
486 **Figure 7, Suppl. Table S1-S2, Suppl. Figure S3E**), which appeared to be a result of
487 depressed thyroid function.

488 - Electrolyte metabolism:

489 Vajreswari showed marked alterations in the erythrocyte's membrane (EM) in
490 kwashiorkor children, while marasmic children were similar to normal children (77). These
491 altered membrane properties included reduced membrane fragility, increased membrane
492 sodium, increased Na⁺/K⁺ pump sites (sodium pump) and increased membrane Na⁺/K⁺-
493 adenosine triphosphatase (ATPase) activity (77). Particularly, the number of Na⁺/K⁺ pump
494 sites per erythrocyte was consistently increased in kwashiorkor but normal in marasmus,
495 (**Grade B - Figure 3, Suppl. Table S1-S2**). In accordance with altered erythrocyte
496 membrane Na⁺/K⁺-ATPase the activity of the sodium pump is increased in kwashiorkor but
497 decreased or normal in marasmus (78). The results suggested that the major changes in
498 membrane Na⁺/K⁺-ATPase were not critical in the pathophysiology of marasmus.
499 Intracellular sodium is high in both kwashiorkor and marasmus; however, this is due to quite
500 different mechanisms. In marasmus this is due to slowing of the sodium pump with decreased
501 sodium efflux whereas the membrane is leaky in kwashiorkor with increased sodium efflux
502 (79); the leak in the membranes can be reproduced experimentally in erythrocytes by

503 depleting them in glutathione to the levels found in kwashiorkor (80) which implicates
504 oxidative stress in the genesis of the electrolytic abnormalities in kwashiorkor.

505 - Inflammatory responses:

506 In 2010, Velasquez showed that children with kwashiorkor had significantly higher
507 concentrations of IL-1 β , IL-6, IL-8, IL-10, and TNF- α in comparison to those with
508 marasmus and suggested that these pro-inflammatory cytokines could be critical biomarkers
509 during infectious process of kwashiorkor (81). By meta-analysis, IL-6 level was consistently
510 higher in the kwashiorkor than in marasmus (**Grade B - Suppl. Table S1-S2, Suppl. Figure**
511 **S3F**). Manary demonstrated that marasmus was associated with an attenuated acute-phase
512 response but not a diminished cytokine response to acute infection, since infected marasmic
513 children had a lower level of acute-phase proteins (CRP) when compared with well-nourished
514 infected children, but the serum cytokine concentrations remained higher (82). The author
515 suggested that acute-phase responses to acute infection are “blunted” in marasmus.
516 Collectively, the available information suggests that the ability to sustain high serum levels of
517 pro-inflammatory cytokines appeared to be maintained in both kwashiorkor and marasmic
518 children. Furthermore, serum concentrations of IgM, IgG and IgA were generally unaffected
519 or modestly increased in severe malnutrition (83).

520 - Liver and pancreas function:

521 In 1948, Waterlow (56), in his study in British West Indian infants, demonstrated fatty
522 infiltration of the liver in oedematous malnutrition for the first time. In contrast, no cells
523 showed fatty change in marasmus (84). Overloading the hepatocytes with fatty acids and the
524 depletion of carnitine suggests that impaired mitochondrial fatty oxidation namely impaired
525 β -oxidation specifically occurs in kwashiorkor. Liver dysfunction in kwashiorkor was also
526 obvious with impaired plasma protein synthesis and export (such as depletion in plasma total
527 protein, albumin, transferrin) and toxic damage to the cells (including increased hepatic iron,

528 produced lipid peroxidation) and by noxious exposures to toxins such as the aflatoxins and
529 aflatoxicol which were not detected in plasma and less frequently in the livers of children
530 with marasmus (85,86).

531 On another hand, histological studies showed that pancreatic fibrosis and pancreatic
532 acinar atrophy were constant features among children with kwashiorkor, but this is also found
533 in children with marasmus, as a non-regular feature (87,88). Like the histological changes,
534 the diminution of serum amylase and lipase are greater in children with kwashiorkor than in
535 those with marasmus (**Grade A and B, respectively - Figure 7, Supp. Table S1-S2, Figure**
536 **S3B**). These pancreatic abnormalities and the high levels of classical markers of hepatic
537 damage, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST),
538 indicate that both the pancreas and the liver are functionally damaged as a characteristic
539 feature of kwashiorkor; these features are much lower or absent in marasmus in most studies.

540 Overall, it is obvious that fatty liver is a dominant feature of kwashiorkor while this
541 feature is much less present in marasmus (73). Depletion in glutathione, serum methionine
542 shortage, excessive free circulating iron with the increase in Na⁺/K⁺ pump sites and cell
543 membrane damage appear to be potentially specific features which can distinguish
544 kwashiorkor from marasmus (**Figure 3, Table 1**).

545 **3.5. Difference in Gut microbiota**

546 - Commensal gut microbiota:

547 In 2013, Gordon suggested a direct link between kwashiorkor and gut microbiota
548 since this phenotype could be transmitted to gnotobiotic mice through faecal microbiota
549 transplantation (89). According to recent studies by Tidjani Alou *et al* (90) and Pham *et al*
550 (91), both kwashiorkor and marasmus are characterized by an altered gut microbiota.

551 Comparing the gut microbiota composition of children with kwashiorkor and
552 marasmus, there was a decrease in total species diversity; in particular there was a

553 predominant loss of anaerobic species in both kwashiorkor and marasmus, but this was
554 always more pronounced in kwashiorkor than in marasmus (91). To our knowledge, only this
555 study compared the gut microbiota of children with marasmus and kwashiorkor. Pham
556 suggested that the gut microbiota status reflects the nutritional status of children with SAM;
557 children with marasmus consistently held an intermediate place between control children and
558 kwashiorkor patients. This is consistent with previous findings on metabolism (**Figure 3;**
559 **Suppl. Table S1-S2**). Also, in the study, the clustering analysis showed that there was a
560 microbiota specific to each form of malnutrition without being altered by age, sex or
561 geographic origin confirming the microbiome as a difference between kwashiorkor and
562 marasmus (91). Furthermore, there was a specific difference at phylum level between
563 kwashiorkor and marasmus. An increase in the proportion of *Proteobacteria* and
564 *Fusobacteria* was only observed in kwashiorkor whereas a decrease in the *Bacteroidetes*
565 proportion occurred only in marasmus, as presented in **Figure 6** (91). For the first time, these
566 findings pointed to another potential specific feature to distinguish kwashiorkor and
567 marasmus based on gut microbiota composition.

568 From our meta-analysis, Aflatoxin (mainly produced by *Aspergillus spp.*) appeared to
569 be specific for kwashiorkor since it was consistently and significantly detected in livers of
570 children with kwashiorkor only (**Figure 3**). From our knowledge, *Aspergillus* and *Candida*,
571 were two of the most recurrent and/or dominant fungal genera inhabiting the human gut,
572 according to metagenomic analysis (92). Future studies focusing on the fungal community
573 should explore the link between these components of the gut microbiota and malnutrition.

574 - Proliferation of pathogenic species:

575 Previously, bacterial overgrowth in the small intestine has been consistently reported
576 in children with malnutrition in the study by Mata in 1972 (34). The only difference noted
577 was that children with severe malnutrition showed more *Enterobacteriaceae* in the small

578 intestine and an altered faecal flora, qualitatively and quantitatively (34). Later, Scragg and
579 Appelbaum showed that the majority of pathogens isolated from blood cultures of
580 malnourished children were Gram-negative (including *Salmonella*, *Escherichia coli*,
581 *Enterobacter cloacae*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*) (93).
582 Particularly, 5 of the 8 children from whose blood salmonellae were isolated had the same
583 type of organism in their stool, suggested a breach in the intestinal barrier in malnourished
584 children (93).

585 Recently, Pham demonstrated that the proliferation of several potentially pathogenic
586 species was observed specifically in kwashiorkor; these included *Klebsiella oxytoca*,
587 *Klebsiella pneumoniae*, *Hafnia alvei*, *Salmonella enterica*, *Gemella haemolysans*,
588 *Enterobacter cloacae*, *Escherichia coli* and *Acinetobacter baumannii* (91). In contrast, none of
589 the bacterial species enriched in marasmus were recognised pathogens (91). Of the 8
590 potentially pathogenic species which were only enriched in the kwashiorkor cases 7 were
591 Gram-negative bacteria whose outer membrane contains lipopolysaccharides (LPS) or
592 endotoxins. The presence of intestinally derived LPS in circulating blood (endotoxemia),
593 particularly at the host-pathogen interface, is considered an important factor in the
594 development of alcoholic hepatitis (94). Recently, Yuan and colleagues reported a high blood
595 alcohol concentration in a NAFLD patient (non-alcoholic fatty liver disease) consuming an
596 alcohol-free, high-carbohydrate diet and demonstrated that certain strains of
597 *Enterobacteriaceae*, especially *Klebsiella pneumoniae* produce high levels of alcohol which
598 could be responsible for the liver pathology (95). Non-alcoholic steatohepatitis (NASH) is
599 associated with proliferation of *Proteobacteria*. It is possible that a similar mechanism occurs
600 in kwashiorkor so that particular gut microbiota bacterial or fungal strains, especially
601 *Klebsiella pneumoniae*, may contribute to the pathogenesis of the liver disease in
602 kwashiorkor through ethanol production in an oxidized (aerobic) atmosphere (96). Moreover,

603 *Escherichia coli* and *Enterobacter cloacae* are bacterial species associated with endotoxin-
604 related obesity and insulin resistance (97,98).

605 Our recent findings in gut microbiota which add to the distinction between
606 kwashiorkor and marasmus have to be reconciled with the known distinctive
607 pathophysiological differences and the place of the microbial changes in the aetiology of
608 kwashiorkor. In particular gram-negative bacteria, especially *Klebsiella pneumoniae* and
609 endotoxemia, in kwashiorkor may contribute to a better understanding of: i) the manifestation
610 of Gram-negative infection in malnourished people; ii) the instrumental role of the intestinal
611 microbiota on the development of obesity (one of the long-term consequences of SAM) in
612 recovered malnourished people; iii) a possible similar process in kwashiorkor pathogenesis
613 and in alcoholic and non-alcoholic fatty liver diseases (NAFLD). This would allow us to
614 initially establish a specific process related to the intestinal microbiota in children affected by
615 kwashiorkor, but also to develop more accurate prognostic evaluation and more effective
616 treatments for severe acute malnutrition.

617 **3.6. Difference in Genetics**

618 In 1968, Gopalan stated that marasmus and kwashiorkor could coexist in the same
619 community where the dietary pattern of the children who developed kwashiorkor or
620 marasmus was not qualitatively different (18). He suggested a potential genetic predisposition
621 might be responsible for the development of kwashiorkor and marasmus in the community. In
622 twin studies of children from rural villages in Malawi (89), during their first 3 years of life,
623 43% of children became discordant for malnutrition with only 7% being concordant for the
624 type of acute malnutrition. Smith didn't find any significant difference between concordance
625 for acute malnutrition and zygosity, neither was there a difference in the number of
626 monozygotic versus dizygotic twin pairs affected with malnutrition, nor a difference in the
627 incidence of discordance for kwashiorkor or marasmus for zygosity (89).

628 After receiving treatment with ready-to-use therapeutic food (RUTF), the gut
629 microbiomes of the healthy co-twins followed the progression of development towards
630 normal older children's microbiota, but the microbiome of their siblings with the kwashiorkor
631 failed to mature (89). Forrester has demonstrated that children who developed marasmus had
632 much lower birth weights than those who developed kwashiorkor and suggested that
633 marasmus was associated with a greater prenatal disadvantage, especially a more restricted
634 in-utero nutritional environment (99). Hanson and Gluckman argued that the foetal response
635 to poor nutrition would induce epigenetic and physiological changes in the children after
636 weaning (100). There are distinct differences in epigenetic imprinting of the genome of
637 children with marasmus and kwashiorkor that persist to adulthood. This finding indicates a
638 "persistent developmentally induced phenomena" mediated by epigenetic processes which
639 may influence the infant's response to acute malnutrition (101). How such epigenetic changes
640 influence the gut microbiota has not been explored to our knowledge.

641 **3.7. Difference in response to Antibiotic Treatment**

642 Since acute bacterial infection is common and serious in severe malnutrition,
643 antibiotics have long been recommended in the treatment of all cases of kwashiorkor and
644 marasmus. But the most suitable antibiotic regimens remained to be discussed: Penicillin was
645 widely used, sometimes with gentamicin, streptomycin or more recently with cephalosporin.
646 There is a proliferation of many *Enterobacteriaceae* species in kwashiorkor, such as
647 *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae* and *Hafniaceae*, including
648 *Hafnia alvei* (91). These species are able to produce β -lactamase to resist penicillin
649 suggesting that penicillin may be suboptimal for the management of kwashiorkor (91).
650 Indeed, Trehan has demonstrated that children receiving cefdinir (a third-generation
651 cephalosporin) had a higher nutritional recovery rate and lower mortality rate than those who
652 received amoxicillin (102). As reported above, endotoxins might be involved in the "similar"

653 pathogenesis of kwashiorkor and NAFLD. Thus, antibiotics with better efficiency against
654 *Enterobacteriaceae* such as cephalosporin or rifaximin emerge as a potential option in
655 antibiotic treatment for kwashiorkor (103).

656 Particularly, our meta-analysis of studies analysing the treatment with antibiotics in
657 malnourished children showed that antibiotics had a different effect on mortality rate in
658 children with or without kwashiorkor (**Grade A - Figure 8A**). Antibiotics (amoxicillin and
659 cefdinir) reduced mortality in children with kwashiorkor and marasmic-kwashiorkor (OR
660 0.48 - 0.55, $p < 0.05$) but did not reduce mortality in children with marasmus (OR 0.98, p
661 $= 0.95$). Furthermore, there was no significant difference in the magnitude of the antibiotic's
662 effect between children with marasmic-kwashiorkor and kwashiorkor ($p = 0.7$). Based on the
663 number need to treat (NNT) calculation, the meta-analysis indicated that to save 1 additional
664 child with marasmic-kwashiorkor, 11 children must be treated (ratio $1/ARR$ (absolute risk
665 reduction) $= 1/0.09$). Similarly, to save 1 child with kwashiorkor, 33 children must be treated
666 ($1/ARR = 1/0.03$). But antibiotics did not save any child with marasmus. The difference
667 between the subgroups was highly significant ($p = 0.0006$).

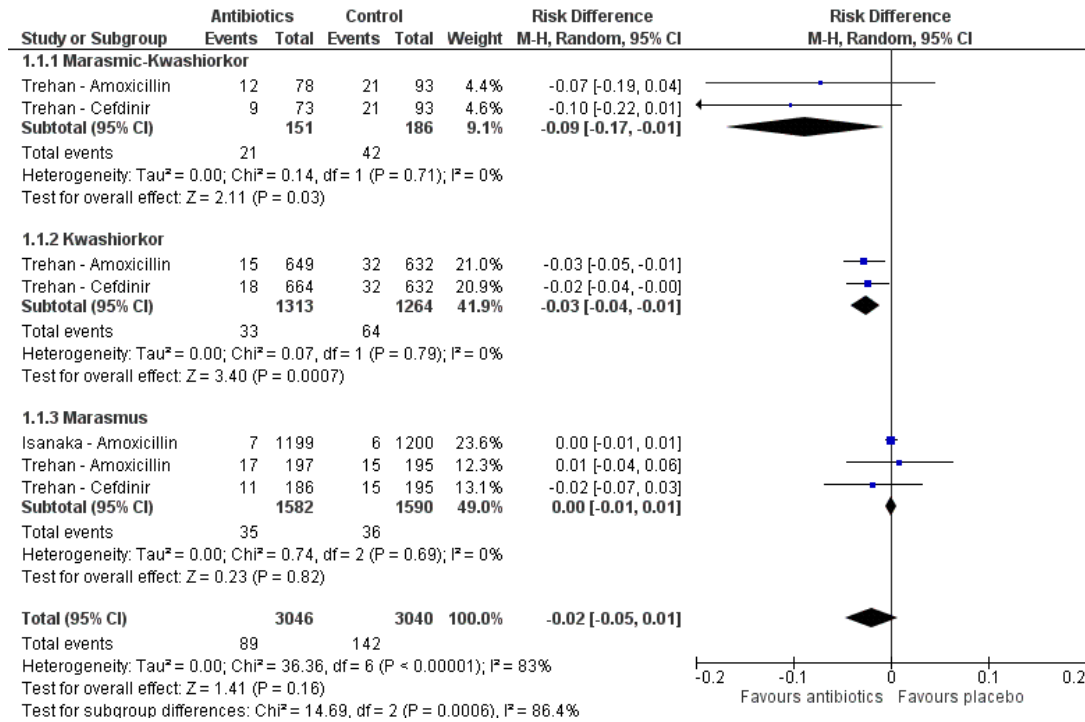
668 Strikingly, Friedland compared mortality associated with bacteraemia in 792 children
669 with severe acute malnutrition (35). By re-analysing their study data, we have confirmed that
670 1 in 4 deaths in the kwashiorkor group was associated with bacteraemia whereas no deaths
671 were associated with bacteraemia in the marasmic group; the attributable fraction in the
672 population was 25% (CI: 15.5 - 32.5) in the oedematous group (kwashiorkor plus marasmic
673 kwashiorkor) versus 2.3% (CI: 2.6 to 7.3) in the non-oedematous/marasmic group. Taken
674 together with the difference in the effect of antibiotics on survival, this suggests that
675 dysbiosis, invasion and bacterial translocation play a major role in the pathogenic process in
676 children with kwashiorkor but has much less effect in children with marasmus. At least 69%
677 of the bacteria isolated in the blood cultures of these children were not sensitive to

678 amoxicillin and only ceftazidime was effective on 100% of the bacteria (35). Both Trehan
679 and Isanaka confirmed that children with severe acute malnutrition significantly gained more
680 weight and recovered more quickly when they received antibiotics. Our meta-analysis
681 showed that antibiotics were significantly and consistently effective for the nutritional
682 recovery of all 3 forms of SAM (marasmic-kwashiorkor, kwashiorkor and marasmus) without
683 a significant difference between groups (**Grade A - Figure 8B**).

684 Overall, the very marked difference in antibiotic treatment on survival of kwashiorkor
685 and marasmic patients was consistent with the proliferation of pathogenic species in
686 kwashiorkor that were not prevalent in marasmic children. This might be important for the
687 specific management of each type of severe malnutrition and promotes more effective
688 treatment and prognosis at least for kwashiorkor. Rationalisation of antibiotic policy in
689 protocols for treating malnutrition is important to reduce mortality, improve recovery and
690 reduce the emergence of resistant pathogens.

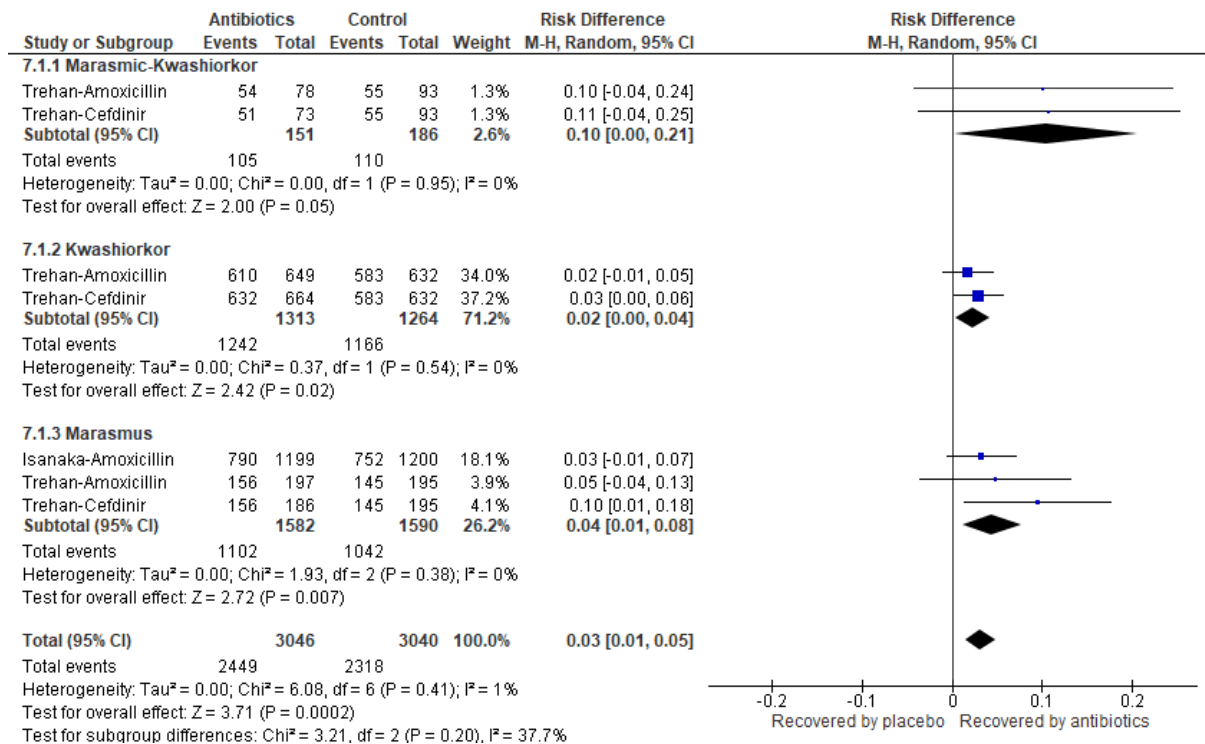
691 **Figure 8: Meta-analysis of studies analyzing the treatment with antibiotics in**
 692 **malnourished children**

693 **A- Effect on mortality rate**



694

695 **B- Effect on nutritional recovery**



696

697

698 **3.8. Difference in Prognosis**

699 The use of updated protocols based upon the pathophysiological studies and the
700 invention of ready-to-use therapeutic foods (RUTF) have successfully reduced mortality in
701 children with severe acute malnutrition (SAM) to “acceptable” levels. However, there is also
702 incomplete restoration to normality, continuing growth retardation (or stunting) and persistent
703 dysbiotic gut microbiota. There may also be long-term consequences such as increased risk of
704 developing metabolic syndrome as adults, but this remains to be investigated.

705 It has been reported that although cases of oedematous malnutrition have a higher
706 mortality and more complications than marasmic children, they recover more rapidly than
707 severely wasted children post-admission (104). According to Galler, the effect of previous
708 marasmus on adolescent’s growth appeared to be more severe, greater in girls than in boys
709 especially in sexual maturation; in contrast in kwashiorkor, neither boys nor girls had deficits
710 in physical growth or sexual maturation (105). Additionally, intellectual performance was
711 found to be impaired in both kwashiorkor and marasmus whereas the persistent deficits in
712 fine motor skills was more extensive in children with histories of kwashiorkor than those of
713 marasmus (106).

714 **4. Conclusions**

715 Severe acute malnutrition is a complex mixture of a number of nutritional conditions
716 that are difficult to disentangle and are still incompletely understood. They are often
717 complicated by various degrees of deficiencies in vitamins and trace minerals that are not
718 normally assessed clinically. This review is not intended to demonstrate the pathogenetic
719 factors of malnutrition, but rather to adopt a systematic arrangement of available information
720 to present a descriptive picture of the differences between kwashiorkor and marasmus
721 (**Figure 6, Table 3, Suppl. Table S2**). Oedema, fatty liver and skin depigmentation are
722 characteristics of kwashiorkor which are much less frequent in marasmus, however in

723 practice there are many patients exhibiting features of both conditions, when they are termed
724 as having “marasmic-kwashiorkor”.

725 The depletion in glutathione, serum methionine shortage, an excessive level of free
726 circulating iron and the increase in Na⁺/K⁺ pump sites appear to be specific features which
727 can distinguish kwashiorkor and rarely occur in marasmus. Some characteristics, such as a
728 decrease in plasma levels of antioxidant proteins (mainly albumin, transferrin and
729 ceruloplasmin), minerals (zinc, copper, selenium) and vitamins (such as vitamin A, C)
730 consistently showed a lower levels in marasmus than occur in healthy children but the levels
731 in kwashiorkor are much lower than in marasmus; this difference was significant by meta-
732 analysis. These changes are consistent with the depletion of anaerobic species in the gut
733 microbiota of malnourished children and are compatible with the oxidative stress which
734 characterises kwashiorkor. In contrast, other characteristics related to body fat mass and poor
735 growth including a decrease in serum leptin and IGF-1 levels are consistently more
736 pronounced in marasmus than kwashiorkor. This is consistent with marasmus being
737 associated with a restricted dietary lacking in type II nutrients (107) with an appropriate
738 adaptive response and a loss of muscle and adipose tissue.

739 Consistent findings of our review suggest that dysbiosis, invasion and bacterial
740 translocation play a major role in the pathogenic process in children with kwashiorkor but to
741 a lesser extent in children with marasmus. Indeed, we only observed enrichment of
742 pathogenic bacteria in the gut of children with kwashiorkor; bacteraemia was responsible for
743 a quarter of deaths in children with a kwashiorkor but no deaths in those with a marasmus in
744 Friedland’s study, and antibiotics improved survival only in children with a kwashiorkor in
745 the studies available for meta-analysis. These results should lead to the early administration
746 of broad-spectrum antibiotics effective on *Proteobacteria*, particularly *Klebsiella*
747 *pneumoniae* (35) in children with kwashiorkor. However, this should not lead to the

748 discontinuation of the recommended amoxicillin for any child with severe acute malnutrition
749 as this treatment is associated with improved nutritional cure in all forms of malnutrition
750 (marasmus, kwashiorkor and kwashiorkor marasmus).

751 The reasons for the difference in bacterial invasion and colonisation in kwashiorkor
752 compared to marasmus need to be established. In kwashiorkor there is a specific reduction in
753 cell surface glycosaminoglycans which form the attachment molecules for many bacteria (for
754 example kwashiorkor children do not get Cholera) (108). The particular reduction in
755 anaerobic species in kwashiorkor may be related to their general oxidised redox of the cells
756 and intestinal contents (49,91,109). Such differences in the intestinal and somatic
757 environment in kwashiorkor may change the spectrum of organisms suited to colonise and
758 infect.

759 The result needs to be confirmed in different geographic situations and patient
760 populations and be related to measures of the disease severity. This is because some of the
761 data are derived from children treated as out-patients that are not critically ill and have a
762 reasonable appetite; nevertheless, the finding is potentially important for the specific
763 management of each type of severe malnutrition that will promote more effective treatment
764 and improve the prognosis for severe malnutrition.

765 Finally, similar characteristics found in kwashiorkor and NAFLD (proliferation of
766 *Proteobacteria*, especially *Klebsiella pneumoniae* which is specifically able to produce
767 ethanol) which suggests a possible similar pathological process in the pathogenesis of
768 kwashiorkor and non-alcoholic steatohepatitis. Such understanding may allow us to formulate
769 treatments that specifically modify the intestinal microbiota of children affected by
770 kwashiorkor and re-establish the compliment of anaerobes and suppress the pathogenic
771 species.

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Table 1: Potential specific characteristics for Kwashiorkor or Marasmus

Characteristics	Kwashiorkor	Marasmus	Confirmed by meta-analysis*
Clinical features			
Oedema	+++		
Depigmentation skin, flag sins, flaky paint, crazy paving	+		
Loss of subcutaneous fat		+	
Dry skin, wrinkled, and loose		+	
Liver			
Enlarged liver	+		
Fatty liver	+		A
Aflatoxin detected in liver	+		A
Biological markers (activity in serum or plasma)			
Glutathione	↓		A
Methionine (Sulfur-containing amino acid)	↓		A
Free circulating iron	↑		C
Na ⁺ /K ⁺ pump sites	↑		B
Gut microbiota			
Pathogenic species proliferation	+		C
Proteobacteria	↑		C
Fusobacteria	↑		C
Bacteroidetes		↓	C
Antibiotics treatment			
Benefit effect of antibiotics treatment on survival	+		A

* Results were classified according to quality of evidence (see Methods). Reference sources were cited in

Suppl. Table S1 in Supplementary data.

Table 2: Mortality rates of Kwashiorkor and Marasmus in studies of malnourished children admitted to hospital

Sources	Marasmus*	Kwashiorkor*	Marasmic-Kwashiorkor*
McLaren, 1969	17.6%	39.9%	28.8%
Van den Broeck, 1993	8%	9%	
Schofeild and Ashworth, 1996	24%	30.1%	32.3%
Bailey, 1963	11%	14%	11%
Munthali, 2015	51%	55%	42%
Wammanda and Adeleke, 2002	21.8%	28.6%	42.9%
Laditan and Tindimebwa, 1983	25%	30%	21.87%
Amsalu and Asnakew, 2006	14.5%	16.9%	28.4%
Trehan, 2016	6.9%	3.2%	14.7%

* Color coded for form of SAM which had the highest mortality rate.

Table 3: Potential specific characteristics for Kwashiorkor or Marasmus

Characteristics	Kwashiorkor	Marasmus	Confirmed by meta-analysis*
Clinical features			
Oedema	+++		
Depigmentation skin, flag sins, flaky paint, crazy paving	+		
Loss of subcutaneous fat		+	
Dry skin, wrinkled, and loose		+	
Liver			
Enlarged liver	+		
Fatty liver	+		A
Aflatoxin detected in liver	+		
Biological markers (activity in serum or plasma)			
Glutathione	↓		A
Methionine (Sulfur-containing amino acid)	↓		A
Free circulating iron	↑		C
Na ⁺ /K ⁺ pump sites	↑		B
Gut microbiota			
Pathogenic species proliferation	+		
<i>Proteobacteria</i>	↑		
<i>Fusobacteria</i>	↑		
<i>Bacteroidetes</i>		↓	
Antibiotics treatment			
Benefit effect of antibiotics treatment on survival	+		A

* Results were classified in category A, B, C, D. Reference sources were cited in Supplementary data