Release Notes 2022-01-03: :
This short letter, with many several self-cites, was motivated by a recent social media exchange [a] [b] and a quick google search did not turn up the name being used in this context before. A couple of newly found citations seemed important enough to justify this summary even if largely redundant with prior work. The cryptic links in the footnotes also highlight the importance of creating bibliographic entries for "works" such as social media posts. TooBib[11] did not immediately work for these and Zotero returned the LinkedIn signup page.
This is a draft and has not been peer reviewed or completely proof read but released in some state where it seems worthwhile given time or other constraints. For information only, not for use for any particular purpose see fuller disclaimers in the text. Caveat Emptor.
I am not a veterinarian or a doctor or health care professional and this is not particular advice for any given situation. Read the disclaimers and take prudent steps to evaluate this information.

[a] https://www.linkedin.com/posts/activity-6882808320126791680-P9Dm
[b] https://www.linkedin.com/feed/update/urn:li:activity:6882808320126791680?commentUrn=urn%3Ali%3Acomment%3A%28activity%3A6882808320126791680%2C6882834187016110080%29&replyUrn=urn%3Ali%3Acomment%3A%28activity%3A6882808320126791680%2C6882984661367320576%29

Missing the B0AT1 : Amino Acid Malnutrition in Aging and SARS-CoV2

Mike Marchywka*
306 Charles Cox , Canton GA 30115
(Dated: January 3, 2022)

The role of amino acid nutrition in covid-19 and common conditions such as aging seems to be ignored when more trendy nutrients or proximal symptoms can be targeted. This may lead to more complicated and less satisfactory results than may be obtained with well motivated causal nutritional interventions. This short editorial reitertaes a concise argument for the investigation of amino acid supplements in a variety of settings.

As new SARS-Cov-2 variants continue to pop-up there is some hope that they will become less virulent to the point of becoming a non-issue. However, in the meantime, there is an ongoing threat to global health. The age-severity curve remains fairly consistent and steep even as some reports of increased hospitalizations among children occur. While significant press is directed towards the virus interaction with ACE2, still little attention is given to the related amino acid transporter B0AT1 . This may be an important part however of long-covid-19 , aging, and other conditions where non-specific symptoms can not otherwise be well resolved. In March 2020, it was suggested that B0AT1 expression may be protective against SARS-Cov-2 in the intestines [16] although more recently it was thought a lung homologue may increase infections [5]. I had posted some notes in July 2020 considering nutrients like tryptophan as being possible issues with covid-19 and aging [10] At about the same time, a preprint from another group compared covid-19 to Hartnup [12] while another group proposed inhibiting B0AT1 hypothesizing it was expressed in the lungs [13]. This illustrates a paradigm where some intervention and its opposite can both be reasonably advocated in the scientific literature. An early case report of covid-19 in a Harthnup patient apparently resolved largely with niacin treatment with the authors noting [14],

> This case serves to raise awareness that SARS-CoV-2 may be altering reabsorption of nutrients in the GI tract and leading to the development of new nutritional deficiencies or exacerbating previously undiagnosed inborn errors of intestinal nutrient absorption.

Some work has been done exploring amino acid blood levels in covid-19 [9] but it may have been a bit discouraging due to no obvious trends towards amino acid depletion from the blood. However, amino acid sensing and response appears to be rather involved [8] (this article is being updated) with blood levels possibly raised due to transport from depots such as muscle to consumers such as the brain. Some feedback mechanisms exist to moderate blood levels such as with tryptophan [7]. By the time the blood levels are low, a catastrophe is probably beginning to manifest. In essence, increased blood quantities are a sign of transport or "stress" and may occur with a decrease in available quantity from normal sources or "quality" as substitutions are made. These kinds of non-monotonic curves are likely a paradigm rather than a paradox.

The comparison to Hartnup may be instructive not just for the result but also the earlier process exploring ACE2 and B0AT1 [1]. Tryptophan was found to mitigate susceptibility to colitis and diarrhea via B0AT1 as early as 2012

*Electronic address: marchywka@hotmail.com; to cite or credit this work, see bibtex in Appendix E

[4] with similar results in pigs where the authors discuss amino acid dynamics [3] similar to considerations I recently outlined [8]. The pig work concentrates on malnourished children who may not have similar covid-19 susceptibility but the differences in detail remain to be elucidated. Tryptophan depletion due to IDO activation may be a specific problem with clinical symptoms depending on other factors. SMVT substrates such as biotin may be one additional issue as epigenetics often comes up [17] in aging with modifications to histones and DNA. Senescence seems to relate to nutrient sensing [2] although cause and effect remain unclear.

The steep and robust age-severity curve for covid-19 provides many unique opportunities to elucidate aging phenomena and maybe resolve some paradoxes. The interaction with ACE2 and B0AT1 , in addition to IDO activation, make it a particularly interesting test case for the role of amino acids in health and disease. Various aspects of these relationships motivate a range of inquiries. Interesting topics include

1. **Aging Clocks** Theories that have developed "biological clocks" or a "biocecemical age" [15] [6] marker should provide a stronger correlation in an age-severity curve or explain why not. Is amino acid sufficiency adequately represented?

2. **Correlates of Age Correlation** What features of SARS-Cov-2 create this age-severity curve that does not seem to apply to most other viruses. Can it be flattened largely with nutrition?

3. **Coagulation and Amino Acid Analogs** Are amino acid analogs produced in areas of ROS generation and do they serve a useful purpose if well contained by, say, clot formation? Not unique to SARS-Cov-2 but coagulopathies and the amino acid balance questions are important

4. **Protein "Quality" in General** Age related modifications, for example AGE's, are well known issues. However, errors at translation (high-infidelity translation) due to amino acid imbalance may not be well explored as causal correlates of infectious disease although viruses often depend on translational quirks. Some literature does exist on translational fidelity and aging.

SARS-Cov-2 presents a unique opportunity to add data to relevant old and new theories. Hopefully floating some languishing topics will avoid "missing the boat" fixating on a few trendy topics.

1. SUPPLEMENTAL INFORMATION

1.1. Computer Code

2. BIBLIOGRAPHY

[1] Simone M.R. Camargo, Dustin Singer, Victoria Makrides, Katja Huggel, Klaas M. Pos, Carsten A. Wagner, Keiji Kuba, Ursula Danilczyk, Flemming Skovby, Robert Kleta, Josef M. Penninger, and Franois Verrey. Tissue-specific amino acid transporter partners ace2 and collectrin differentially interact with hartnup mutations. *Gastroenterology*, pages 872–882.e3, 10 2008. URL: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7094282/, doi:10.1053/j.gastro.2008.10.055.

[2] Bernadette Carroll and Viktor I. Korolchuk. Nutrient sensing, growth and senescence. *The Febs Journal*, pages 1948–58, 02 2018. URL: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC6001427/, doi:10.1111/febs.14400.

[3] David D. Fischer, Sukumar Kandasamy, Francine C. Paim, Stephanie N. Langel, Moyasar A. Alhamo, Lulu Shao, Juliet Chepngeno, Ayako Miyazaki, Huang-Chi Huang, Anand Kumar, Gireesh Rajashekara, Linda J. Saif, and Anastasia N. Vlasova. Protein malnutrition alters tryptophan and angiotensin-converting enzyme 2 homeostasis and adaptive immune responses in human rotavirus-infected gnotobiotic pigs with human infant fecal microbiota transplant. *Clinical and Vaccine Immunology*, 24, 8 2017. URL: http://dx.doi.org/10.1128/cvi.00172-17, doi:10.1128/cvi.00172-17.

[4] Tatsuo Hashimoto, Thomas Perlot, Ateequr Rehman, Jean Trichereau, Hiroaki Ishiguro, Magdalena Paolino, Verena Sigl, Toshikatsu Hanada, Reiko Hanada, Simone Lipinski, Birgit Wild, Simone M. R. Camargo, Dustin Singer, Andreas Richter, Keiji Kuba, Akiyoshi Fukamizu, Stefan Schreiber, Hans Clevers, Francois Verrey, Philip Rosenstiel, and Josef M. Penninger. Ace2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature*, 487, 07 2012. URL: https://www.nature.com/articles/nature11228, doi:10.1038/nature11228.

[5] Cody B. Jackson, Michael Farzan, Bing Chen, and Hyeryun Choe. Mechanisms of sars-cov-2 entry into cells. *Nature Reviews Molecular Cell Biology*, 23, 10 2021. URL: https://www.nature.com/articles/s41580-021-00418-x, doi:10.1038/s41580-021-00418-x.

[6] S. Michal Jazwinski and Sangkyu Kim. Examination of the dimensions of biological age. *Frontiers in Genetics*, 03 2019. URL: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC6445152/, doi:10.3389/fgene.2019.00263.

[7] Simon Klaessens, Vincent Stroobant, Delia Hoffmann, Mads Gyrd-Hansen, Luc Pilotte, Nathalie Vigneron, Etienne De Plaen, and Benoit J. Van den Eynde. Tryptophanemia is controlled by a tryptophan-sensing mechanism ubiquitinating tryptophan 2,3-dioxygenase. *Proceedings of the National Academy of Sciences*, 118(23), 2021. URL: https://www.pnas.org/content/118/23/e2022447118, arXiv:https://www.pnas.org/content/118/23/e2022447118.full.pdf, doi:10.1073/pnas.2022447118.

[8] Mike J Marchywka. The paradox paradigm: When could amino acid supplements be beneficial? techreport MJM-2021-015, not institutionalized, independent, 306 Charles Cox , Canton GA 30115, 12 2021. URL: https://www.researchgate.net/publication/357250784_The_Paradox_Paradigm_When_Could_Amino_Acid_Supplements_Be_Beneficial.

[9] Mike J Marchywka. Update to covid-19 age distribution notes. Technical Report MJM-2021-007, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, 8 2021. Version .1, may change signficantly if less than 1.00. URL: https://www.researchgate.net/publication/353946686_Draft_table_comparing_expectations_to_recent_results_with_covid-19.

[10] M.J. Marchywka. On the age distribution of sars-cov-2 patients. Technical Report MJM-2020-002-0.10, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, 7 2020. Version 0.10 , may change signficantly if less than 1.00. URL: https://www.linkedin.com/posts/marchywka_notes-on-aging-as-it-relates-to-covid19-activity-6684083706170265601-JMnN.

[11] M.J. Marchywka. Impromptu bibtex find and merge tool. Technical Report MJM-2021-002, not institutionalized , independent, 306 Charles Cox , Canton GA 30115, 01 2021. Version 0.1.1 , may change signficantly if less than 1.00. URL: https://www.researchgate.net/publication/350608962_toobib.

[12] Enzo Nisoli, Saverio Cinti, and Alessandra Valerio. Covid-19 and hartnup disease: an affair of intestinal amino acid malabsorption. *Eating and Weight Disorders*, pages 1–5, 07 2020. URL: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7369504/, doi:10.1007/s40519-020-00963-y.

[13] Mariafrancesca Scalise and Cesare Indiveri. Repurposing nimesulide, a potent inhibitor of the b0at1 subunit of the sars-cov-2 receptor, as a therapeutic adjuvant of covid-19. *SLAS DISCOVERY: Advancing the Science of Drug Discovery*, 25, 06 2020. URL: http://dx.doi.org/10.1177/2472555220934421, doi:10.1177/2472555220934421.

[14] Christopher Tanchez, Pardeep Taunk, Neera Sinha, and John W. Trillo. S2044a rare case of severe acute respiratory syndrome coronavirus 2 (sars-cov-2)-induced hartnup disease. *American Journal of Gastroenterology*, 115, 10 2020. URL: http://dx.doi.org/10.14309/01.ajg.0000710224.64421.53, doi:10.14309/01.ajg.0000710224.64421.53.

[15] Julia W. Wu, Amber Yaqub, Yuan Ma, Wouter Koudstaal, Albert Hofman, M. Arfan Ikram, Mohsen Ghanbari, and Jaap Goudsmit. Biological age in healthy elderly predicts aging-related diseases including dementia. *Scientific Reports*, 11, 08 2021. URL: https://www.nature.com/articles/s41598-021-95425-5, doi:10.1038/s41598-021-95425-5.

[16] Renhong Yan, Yuanyuan Zhang, Yaning Li, Lu Xia, Yingying Guo, and Qiang Zhou. Structural basis for the recognition of sars-cov-2 by full-length human ace2. *Science*, 367, 03 2020. URL: http://dx.doi.org/10.1126/science.abb2762, doi:10.1126/science.abb2762.

[17] Janos Zempleni, Yousef I Hassan, and Subhashinee SK Wijeratne. Biotin and biotinidase deficiency. *Expert review of endocrinology & metabolism*, pages 715–24, Nov 2008. URL: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC2726758/, doi:10.1586/17446651.3.6.715.

Acknowledgments

1. Pubmed eutils facilities and the basic research it provides.

2. Free software including Linux, R, LaTex etc.

3. Thanks everyone who contributed incidental support.

Appendix A: Statement of Conflicts

No specific funding was used in this effort and there are no relationships with others that could create a conflict of interest. I would like to develop these ideas further and have obvious bias towards making them appear successful. Barbara Cade, the dog owner, has worked in the pet food industry but this does not likely create a conflict. We have no interest in the makers of any of the products named in this work.

Appendix B: About the Authors and Facility

This work was performed at a dog rescue run by Barbara Cade and housed in rural Georgia. The author of this report ,Mike Marchywka, has a background in electrical engineering and has done extensive research using free online literature sources. I hope to find additional people interested in critically examining the results and verify that they can be reproduced effectively to treat other dogs.

Appendix C: Symbols, Abbreviations and Colloquialisms

TERM definition and meaning

Appendix D: General caveats and disclaimer

This document was created in the hope it will be interesting to someone including me by providing information about some topic that may include personal experience or a literature review or description of a speculative theory or idea. There is no assurance that the content of this work will be useful for any paricular purpose.

All statements in this document were true to the best of my knowledge at the time they were made and every attempt is made to assure they are not misleading or confusing. However, information provided by others and observations that can be manipulated by unknown causes ("gaslighting") may be misleading. Any use of this information should be preceded by validation including replication where feasible. Errors may enter into the final work at every step from conception and research to final editing.

Documents labelled "NOTES" or "not public" contain substantial informal or speculative content that may be terse and poorly edited or even sarcastic or profane. Documents labelled as "public" have generally been edited to be more coherent but probably have not been reviewed or proof read.

Generally non-public documents are labelled as such to avoid confusion and embarassment and should be read with that understanding.

Appendix E: Citing this as a tech report or white paper

Note: This is mostly manually entered and not assured to be error free.
This is tech report MJM-2022-001.

Version	Date	Comments
0.01	2022-01-01	Create from empty.tex template
0.5	2022-01-03	first draft
-	January 3, 2022	version 0.50 MJM-2022-001
1.0	20xx-xx-xx	First revision for distribution

Released versions,
build script needs to include empty releases.tex

Version	Date	URL
0.50	2022-01-03	https://www.researchgate.net/publication/357538275_Missing_the_B0AT1_Amino_Acid_Malnutrition_in_Aging
0.50	2022-01-03	https://www.academia.edu/s/5ef2261639

@techreport{marchywka-MJM-2022-001-0.50 ,
filename =”hartnup” ,
run-date =”January 3, 2022” ,
title =”Missing the B0AT1 : Amino Acid Malnutrition in Aging and SARS-CoV2” ,
author =”Mike J Marchywka ” ,
type =”techreport” ,
name =”marchywka-MJM-2022-001-0.50 ” ,
number =”MJM-2022-001” ,
version =”0.50 ” ,
institution =”not institutionalized, independent ” ,
address =” 306 Charles Cox , Canton GA 30115” ,
date =”January 3, 2022” ,
startdate =”2022-01-01” ,
day =”3” ,
month =”1” ,
year =”2022” ,
author1email =”marchywka@hotmail.com” ,
contact =”marchywka@hotmail.com” ,
author1id =”orcid.org/0000-0001-9237-455X” ,
pages =” 6”
}

Supporting files. Note that some dates,sizes, and md5's will change as this is rebuilt.

This really needs to include the data analysis code but right now it is auto generated picking up things from prior build in many cases

```
3511 Jan 3 13:40 comment.cut 4216f3868bc9f60ed56d91dafa396df1
1101 Aug 15 2019 /etc/texmf/web2c/texmf.cnf af7716885e081ab43982cab7b4672c1a
4072 Jan 3 13:40 hartnup.aux 23a6fd26f52c29c78c50cde265b2204c
8381 Jan 3 13:40 hartnup.bbl a6a4c44e22a53d34683a0ed73baffe00
39558 Jan 3 13:40 hartnup.bib f31f363e4294eef9b6fd37a7539b6387
1209 Jan 3 13:40 hartnup.blg ebf7f9dbd556b4e9f80f80db319dea26
0 Jan 3 13:40 hartnup.bundle_checksums d41d8cd98f00b204e9800998ecf8427e
29459 Jan 3 13:40 hartnup.fls 53c1887a26bbc9ad778900f89e8b7f3c
2 Jan 3 13:40 hartnup.last_page 9ae0ea9e3c9c6e1b9b6252c8395efdc1
58503 Jan 3 13:40 hartnup.log 489492cbad90924e7454380351fcae7e
616 Jan 3 13:40 hartnup.out 58842cfbc062d69121c094a77cc098c6
205826 Jan 3 13:40 hartnup.pdf f151e5b256b9552cec9a6e284ae54940
21888 Jan 3 13:39 hartnup.tex b6c865648e543b6c84c5e1122cdc2e02
26173 Jan 1 05:53 /home/documents/latex/bib/mjm_tr.bib 212f1579e97dce04508fccbe61eddb49
26023 Jan 2 17:24 /home/documents/latex/bib/releases.bib 9242b8f73c407fa1f1e9cead404b893a
7331 Jan 24 2019 /home/documents/latex/pkg/fltpage.sty 73b3a2493ca297ef0d59d6c1b921684b
7434 Oct 21 1999 /home/documents/latex/pkg/lgrind.sty ea74beead1aa2b711ec2669ba60562c3
7162 Nov 13 2015 /home/documents/latex/pkg/mol2chemfig.sty f5a8b1719cee30a4df0739275ac75f8a
1069 Oct 15 19:43 /home/documents/latex/share/includes/disclaimer-gaslight.tex 94142
    bbe063984d082bff3b400abe0fb
425 Oct 11 2020 /home/documents/latex/share/includes/disclaimer-status.tex b276f09e06a3a9114f927e4199f379f7
1403 Dec 4 20:31 /home/documents/latex/share/includes/mjmaddbib.tex 8e515fcae10a0e8a83e7c7cb0a2b633a
3158 Jan 1 12:12 /home/documents/latex/share/includes/mycommands.tex 05fc6e677a04a995854a9c8d4f6504e8
2901 Jun 17 2020 /home/documents/latex/share/includes/myskeletonpackages.tex
    fcfcd2e3c8d69d533932edaaa47f53a1
1538 Aug 14 07:26 /home/documents/latex/share/includes/recent_template.tex 49763d2c29f74e4b54fa53b25c2cc439
940 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/cmextra/cmex7.tfm
    f9e66c0105a30e64e3a0f5c4f79efb8d
852 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msam10.tfm
    b4a46d2c220ee4ffaaf87c608f8593cd
860 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msam5.tfm
    c4142ffef6136ff95621fbe99efb7cec
864 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msam7.tfm 2998
    d813a00ebf21070684f214a50f7e
844 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msbm10.tfm
```

```
    f7721eee07bdc9e743e6c5f3f7e3d06d
876 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msbm5.tfm 9
    e3df3efef7afc4b0381e88a6402f777
876 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/amsfonts/symbols/msbm7.tfm 374365713297
    d597717720c5786882e5
1260 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmbx12.tfm 41596a2c763cf972bbdd853b378ec55a
1264 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmbx9.tfm c3f8c3f0292777e1e9153581c59f8506
1448 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmmi6.tfm be0f1d444547257aeb3f042af14f3e47
1456 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmmi8.tfm e7bb485e28fc530112b40f5c89496200
1224 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmr12.tfm 48d5728dc6473917c0e45f34e6a0e9cd
1236 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmr6.tfm 63e3c1344d1e22a058a5cb87731337e0
1228 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmr8.tfm 29a15bf51bfb16348a5cabb3215cf3fd
1228 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmr9.tfm b0280c40050dc3527dafc7c425060d31
1052 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmsy6.tfm 00c03700e0e2f29cde6c0b50a5c56df5
1056 Jul 24 2019 /home/marchywka/.texmf-var/fonts/tfm/public/cm/cmsy8.tfm 7ef80e56d3b9e223d3bce5a9065b95ad
39155 Jan 3 13:37 non_pmc_hartnup.bib 24239baa618d3bd43e977c8d1439b0d1
429 Jan 3 13:40 releases.tex 1df1a69d2c126aacb86525306f1fed9a
31050 Jul 21 2011 /usr/share/texlive/texmf-dist/bibtex/bst/urlbst/plainurl.bst
    ffdaefb09013f5fd4b31e485c13933c1
15 Jul 23 2019 /var/lib/texmf/fonts/map/pdftex/updmap/pdftex.map -> pdftex_dl14.map 341
    e900b5c25cd7029252688d79936e4
1431330 Jul 23 2019 /var/lib/texmf/web2c/pdftex/pdflatex.fmt c2a1d33979bfd7080ba601d397e5e158
205826 Jan 3 13:40 hartnup.pdf f151e5b256b9552cec9a6e284ae54940
```