BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-027767.R1
Article Type:	Communication article
Date Submitted by the Author:	10-Dec-2018
Complete List of Authors:	Leese, Henry; University of Hull, Hull York Medical School Sathyapalan, Thozhukat; Hull Royal Infirmary, Diabetes and Endocrinology Allgar, Victoria; York University, HYMS/Health Sciences Brison, Daniel; Central Manchester University Hospitals NHS Foundation Trust, Department of Reproductive Medicine Sturmey, Roger; University of Hull, Hull York Medical School
Primary Subject Heading:	Medical publishing and peer review
Secondary Subject Heading:	Medical education and training, Research methods
Keywords:	STATISTICS & RESEARCH METHODS, Data analysis and interpretation, Data distributions

Going to extremes: the Goldilocks/Lagom principle and data distribution

Henry J Leese [1*], Thozhukat Sathyapalan [2,3], Victoria Allgar [4], Daniel R Brison [5,6] & Roger G Sturmey [1]

1, Centre for Atherothrombosis and Metabolism, Hull York Medical School, University of Hull, Hull, HU6 7RX, UK

2, Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, Hull, HU6 7RK UK

3, Department of Endocrinology, Hull and East Yorkshire Hospitals NHS Trust, Hull, UK

4, Hull York Medical School, University of York, York YO10 5DD, UK

5, Maternal and Fetal Health Research Centre, Division of Developmental Biology and Medicine, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Sciences Centre, St. Mary's Hospital, Manchester, M13 9WL, United Kingdom

6, Department of Reproductive Medicine, St. Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, M13 9WL, United Kingdom

* To whom correspondence should be addressed: henry.leese@hyms.ac.uk

Abstract

Numerical data in biology and medicine are commonly presented as mean or median with error or confidence limits, to the exclusion of individual values. Analysis of our own and others' data indicates that this practice risks excluding 'Goldilocks' effects in which a biological variable has a range of expression between 'too much' and 'too little' with a region in between where its function is 'just right', or as termed in Sweden, 'Lagom', which symbolises 'moderation' and 'in balance. This was confirmed by a narrative search of the literature using the PubMed Database, which revealed numerous relationships of biological and clinical phenomena of the Goldilocks/Lagom form including quantitative and qualitative examples from the health and social sciences. Some possible mechanisms underlying these phenomena are considered. We conclude that retrospective analysis of existing data will most likely reveal a vast number of such distributions to the benefit of medical understanding and clinical care and that a transparent approach of presenting each value within a data set individually should be adopted to ensure a more complete evaluation of research studies in future.

174 words

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Text

Introduction

Numerical data in science and medicine have traditionally been presented as mean or median values with standard errors or standard deviations. Such data commonly take the form of tables, bar graphs or line graphs. However, as (1) point out, this practice poses a problem since different distributions of data can lead to the same bar or line graph. This was well illustrated recently by (2) who used illustrative data from a hypothetical experiment to examine the impact of three different cell lines on drug receptor activation and showed that a variety of distributions of individual data points can lead to similar bar graphs with the same mean (Fig 1).

The attention paid to individual variation in cellular and molecular biological and clinical studies is relatively recent, but has been well-known for many years to ecologists, especially following the publication by Albert F. Bennett, in 1987, of an influential article entitled: *Inter-individual variability: an underutilized resource*'. Bennett, an ecological physiologist, pointed out that mean values with confidence intervals about the mean, once published tend to *'-- take on a life of their own, and become the only point of analysis and comparison'* to the exclusion of the individual values, and their potential significance. Bennett referred to this tendency as *'the tyranny of the Golden Mean',* and as an alternative, advocated the analysis of inter-individual variability, i.e., the full range of individual values, he considered could provide the observer with a greater interpretative repertoire.

In the time since Bennett's paper, there has been a movement away from the tyranny of the mean in many areas of biology, notably in ecology (3). Examples are provided by Stephen J Gould (4), who wrote an article on '*The median isn't the message'*, Hayes and Jenkins (5) on individual variation in mammals, and Lloyd-Smith (6) on the spread of epidemics of human disease.

Our interest in inter-individual variability arose particularly from research in which we have been involved on (a) the development and metabolism of single preimplantation mammalian embryos (DB, HL, RS) and (b) of glycaemic control in individual human subjects (TS).

(a) Development and metabolism of single preimplantation embryos

Data which illustrate the value of distributions rather than mean or median values were provided by (7) who measured the consumption of the essential nutrient, pyruvate, by single bovine preimplantation embryos at the zygote stage (1-cell fertilised egg; day 1 of development). The experiments revealed considerable heterogeneity between individual embryos such that it was possible to divide them prospectively into 3 groups - of 'high', 'intermediate' and 'low' pyruvate consumption at an early stage (day 2) - and track their subsequent development to the blastocyst stage, a critical developmental endpoint. These

data indicated that intermediate values of pyruvate consumption correlated with viability (capacity to form a blastocyst), though with considerable overlap between the categories. Put another way, which takes account of this overlap, plotting individual values revealed the existence of an optimal 'range' of metabolic activity. This concept was developed in a follow-up paper (8) in which we proposed that the optimal range was equivalent to a 'Goldilocks zone' or as it is known in Sweden, of 'lagom', meaning 'just the right amount', in which embryos with maximum developmental potential are located (see a*).

(b) Glycaemic control

Plasma Haemoglobin A_{1c} (HbA1c) is the standard measure of glucose control and is recommended for use as a diagnostic test for humans with diabetes mellitus (9). There is an association between the extent of high blood glucose as measured by HbA_{1c} and the risk of death and of macrovascular and microvascular disease in patients with type 2 diabetes (T2DM) (10). In the landmark United Kingdom Prospective Diabetes Study, intensive glycaemic control aiming for a lower HbA_{1c} of 7% was associated with improved outcome in newly diagnosed patients with type 2 diabetes (T2DM) (11). This finding was then extrapolated to all patients with T2DM, and as a result, low HbA1c levels were recommended for management of patients with T2DM. However, concerns arose as data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial began to emerge showing increased all-cause mortality and cardiovascular mortality in the intensive treatment group who were treated with antihyperglycaemic agents aiming for a lower HbA_{1c} target of 6% compared with conventional antihyperglycaemic treatment in patients with T2DM aiming for HbA_{1c} of 7-7.9%. These results led to early termination of the trial (12). Further studies have demonstrated that both high and low levels of HbA1c are associated with an increased risk of all-cause mortality suggesting a "Goldilocks' or 'lagom" state in between.

Similar "U" shaped associations with HbA1c and all-cause mortality have also been shown for type 1 diabetes (13). Even in patients without diabetes, extremes of glycaemia as measured by HbA1c are associated with adverse clinical outcomes including cardiovascular events and all-cause mortality. Similar increases in mortality in either extremes are seen with body weight, blood pressure, birth weight, cholesterol and other cardiovascular risk factors.

Goldilocks and Lagom

The Goldilocks zone has been defined mathematically by (14) in the context of xenobiotic ligand binding to nuclear receptors as a *'Non-monotonic receptor-mediated dose-response*

curve' (NMDRC), and by (15) in the context of endocrine disrupting chemicals as '*a response where the slope of the curve changes sign from positive to negative or vice versa somewhere along the range of doses examined*'. These are valuable definitions because they can be applied to all non-linear distributions including U-shaped, inverted U-shaped, J-shaped, sigmoidal and reverse sigmoidal.

The U-shaped curve is probably the most widely observed. It usually refers to the nonlinear relationship between two variables, in particular, a dependent and an independent variable. Because many analytical methods assume an underlying linear relationship, systematic deviation from linearity can lead to bias in estimation of safe levels in exposure to nutrients, drugs or toxic agents (for a discussion see section on *Mechanisms* below and (15)).

How widespread is the presence of a Goldilocks zone in biology and medicine?

We thought it might be instructive to discover how widely the notion of a 'Goldilocks zone' is a feature of the wider biological literature, especially as applied to medicine. A comprehensive search for information conducted on the *PubMed* database in early 2018 using the term 'Goldilocks' revealed 184 entries, all of which have been examined, together with the grey literature. Only articles in English language were selected. A selection of 43 of these publications has been presented (Appendix 1) as representative of the range of phenomena which invoke the Goldilocks concept in order to increase biological and clinical understanding. It should be emphasised that this is a narrative review rather than systematic review and no judgement on the quality of these studies or of those which have been omitted is implied. Patient/public involvement: No members of the public, nor patients were involved in the synthesis of this manuscript.

Inspection of these examples reveals the wide range of biological and clinical phenomena in which Goldilocks zones have been found including the health and social sciences which can be qualitative rather than quantitative. It seems likely that a vast number remain to be discovered and that authors could, in a relatively simple manner, derive added value from their existing data by presenting distributions rather than median/mean values, and making raw data available to the research community via online repositories. This would allow systematic re-analysis by data scientists with an interest in the Goldilocks/Lagom concept.

Mechanisms underlying the Goldilocks Principle and what is Lagom

Mechanisms which are global in scope

We previously proposed an explanation that may account for Goldilocks/Lagom phenomena, derived from our work on energy efficiency in early mammalian embryo development (8) which made use of an account of general aspects of biological optimisation by (16). The premise was that living things aim to function with the minimum input of energy, i.e., with high energetic efficiency. To accomplish this will obviously require a threshold level of metabolic activity to ensure a given process proceeds physiologically, while the upper limit will be set by the capacity to increase metabolism vs '*the energy parsimony in almost everything (*living things*) do*' (16). The Goldilocks/Lagom zone will obviously lie between these extremes. The boundaries will be set by homeostatic mechanisms at all levels of organisation. Such boundaries will be flexible in order to allow for the capacity to up- or down-regulate metabolism in response to stress. Responses of these types have been usefully categorised by ecologists to distinguish (a) modest changes in metabolism (up or down within the *optimum* (Goldilocks/Lagom) range) from which the cell/organism can recover (the so-called *Pejus* range) and (b) extreme perturbation beyond the optimum which shifts metabolism irreversibly into a *Pessimum* range which is fatal (see Fig 2 in (17)

Some *specific mechanisms* for the production of non-monotonic receptor-mediated dose-response curves (NMDRCs) were well summarised by (15) in terms of the effect of endocrine disrupting chemicals, notably Bisphenol A on cells in culture, whole organisms, laboratory animals and human populations. Interestingly, it was reported that NMDRCs were common, comprising 20-30% of all studies examined, depending on the conditions; e.g., in vivo vs in vitro. Mechanisms considered included cytotoxicity (18), inhibition of cell proliferation (19); hormone receptors produced vs degraded (20); cell and tissue specific co-factors (21) and pharmacological effects. At the whole body level, examples of NMDRCs in nutrition are widespread, reflecting minimum requirments at the lower end of the distribution and toxicity at the higher, for example, vitamin A. Vandenberg (15) concludes that *'strong evidence for Non-monotonic receptor-mediated dose-response curves' - - question the current risk assessment practice where 'safe' levels are predicted from high dose exposures'*

Conclusion

There has long been a fixation in the biological and clinical research communities with presenting data solely as measures of dispersion (means and medians) and of central tendency (e.g., standard deviation and interquartile range). We believe that the retrospective

analysis of existing data could reveal numerous potential relationships with a Goldilocks/Lagom pattern.

Interestingly, the editors of the British Journal of Pharmacology ' (2) '*will now require that, where possible, numerical data (whether categorical or continuous), particularly involving two sets or paired data, should be presented using scatter-plots, before-after graphs, and other forms in which each individual 'n' value is individually plotted, rather than using bar charts. Authors presenting data as bar charts should state that a scatter plot or before–after charts did not reveal unusual or interesting aspects of the data not obvious from the bar chart'.*

We believe the Journal should be complimented on this approach and urge all such journals to adopt it.

Author contributions:

H J Leese; conceived the study, conducted literature searches and wrote the first draft. All authors then commented on subsequent drafts. V Allgar; provided statistical advice, DR Brison; contributed to the initial concept and provided new material, as did RG Sturmey who also prepared the manuscript for submission T Sathyalapan; contributed to initial concept; provided new material and clinical expertise

Competing Interests:

The authors have no competing interests to declare in relation to this work.

Funding:

No specific funding was awarded for this research.

References

1. Weissgerber TL, Milic NM, Winham SJ, Garovic VD. Beyond Bar and Line Graphs: Time for a New Data Presentation Paradigm. PLoS Biol. 2015;13(4):1–10.
2. George CH, Stanford SC, Alexander S, Cirino G, Docherty JR, Giembycz MA, et al. Updating the guidelines for data transparency in the British Journal of Pharmacology - data sharing and the use of scatter plots instead of bar charts. Br J Pharmacol [Internet]. 2017 Sep 1 [cited 2018 Oct 4];174(17):2801–4. Available from: http://doi.wiley.com/10.1111/bph.13925
3. Roche DG, Careau V, Binning SA. Demystifying animal "personality" (or not): why individual variation matters to experimental biologists. J Exp Biol [Internet]. 2016 Dec 15 [cited 2018 Oct 4];219(Pt 24):3832–43. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/27852750

4. Gould SJ. The Median Isn't the Message [Internet]. [cited 2018 Oct 4]. Available from: https://people.umass.edu/biep540w/pdf/Stephen Jay Gould.pdf

5. Hayes JP, Jenkins SH. Individual Variation in Mammals. J Mammal [Internet]. 1997 May 21 [cited 2018 Oct 4];78(2):274–93. Available from: https://academic.oup.com/jmammal/article-lookup/doi/10.2307/1382882

6. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. Nature [Internet]. 2005 Nov 17 [cited 2018 Oct 4];438(7066):355–9. Available from: http://www.nature.com/articles/nature04153

7. Guerif F, McKeegan P, Leese HJ, Sturmey RG. A Simple Approach for COnsumption and RElease (CORE) Analysis of Metabolic Activity in Single Mammalian Embryos. PLoS One. 2013;8(8).

8. Leese HJ, Guerif F, Allgar V, Brison DR, Lundin K, Sturmey RG. Biological optimization, the Goldilocks principle, and how much is lagom in the preimplantation embryo. Mol Reprod Dev. 2016;83(9).

9. American Diabetes Association AD. Diagnosis and classification of diabetes mellitus. Diabetes Care [Internet]. 2011 Jan 1 [cited 2018 Oct 4];34 Suppl 1(Supplement 1):S62-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21193628

10. Khaw K-T, Wareham N. Glycated hemoglobin as a marker of cardiovascular risk. Curr Opin Lipidol [Internet]. 2006 Dec [cited 2018 Oct 4];17(6):637–43. Available from: https://insights.ovid.com/crossref?an=00041433-200612000-00006

11. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet [Internet]. 1998 Sep 12 [cited 2018 Oct 4];352(9131):837–53. Available from: https://www.sciencedirect.com/science/article/pii/S0140673698070196?via%3Dihub

12. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. N Engl J Med [Internet]. 2009 Jan 8 [cited 2018 Oct 4];360(2):129–39. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa0808431

13. Schoenaker DAJM, Simon D, Chaturvedi N, Fuller JH, Soedamah-Muthu SS. Glycemic Control and All-Cause Mortality Risk in Type 1 Diabetes Patients: The EURODIAB Prospective Complications Study. J Clin Endocrinol Metab [Internet]. 2014 Mar 1 [cited 2018 Oct 4];99(3):800–7. Available from: https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2013-2824

14. Kohn MC, Melnick RL. Biochemical origins of the non-monotonic receptor-mediated dose-response [Internet]. Vol. 29, Journal of Molecular Endocrinology. 2002 [cited

2018 Oct 4]. Available from: http://www.endocrinology.org

15. Vandenberg LN. Non-monotonic dose responses in studies of endocrine disrupting chemicals: bisphenol a as a case study. Dose Response [Internet]. 2014 May [cited 2018 Oct 4];12(2):259–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24910584

16. Johnson AT. Teaching the principle of biological optimization. J Biol Eng [Internet]. 2013 Feb 20 [cited 2018 Oct 4];7(1):6. Available from: http://jbioleng.biomedcentral.com/articles/10.1186/1754-1611-7-6

17. Sokolova IM. Energy-Limited Tolerance to Stress as a Conceptual Framework to Integrate the Effects of Multiple Stressors. Integr Comp Biol [Internet]. 2013 Oct 1 [cited 2018 Oct 4];53(4):597–608. Available from: https://academic.oup.com/icb/article-lookup/doi/10.1093/icb/ict028

18. Welshons W V, Thayer KA, Judy BM, Taylor JA, Curran EM, Vom Saal FS. Large Effects from Small Exposures. I. Mechanisms for Endocrine-Disrupting Chemicals with Estrogenic Activity. 2003 [cited 2018 Oct 8];111. Available from: http://dx.doi.org/

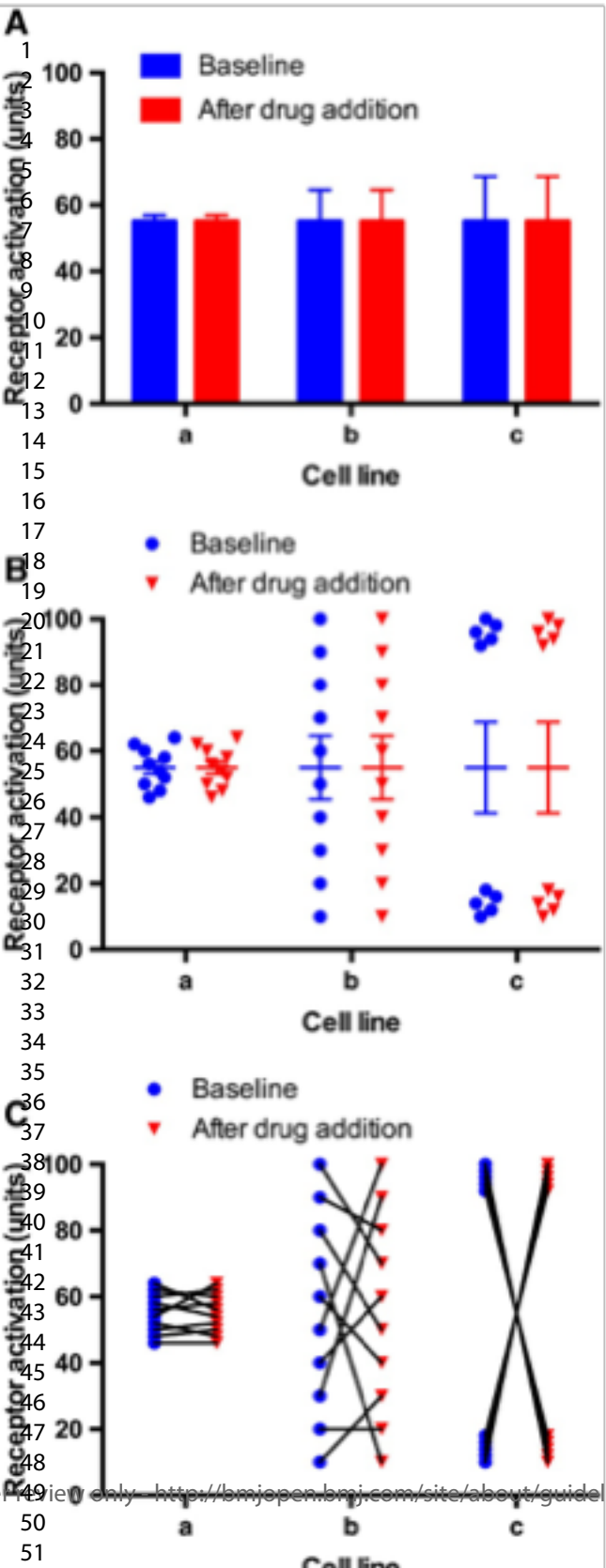
19. SOTO AM, SONNENSCHEIN C, PRECHTL N, WEILL B, OLEA N. Methods to Screen Estrogen-Agonists and Antagonists. J Med Food [Internet]. 1999 Jan [cited 2018 Oct 8];2(3–4):139–42. Available from: http://www.liebertpub.com/doi/10.1089/jmf.1999.2.139

20. Ismail A, Nawaz Z. Nuclear hormone receptor degradation and gene transcription: An update. IUBMB Life (International Union Biochem Mol Biol Life) [Internet]. 2005 Jul 1 [cited 2018 Oct 8];57(7):483–90. Available from: http://doi.wiley.com/10.1080/15216540500147163

21. Jeyakumar M, Webb P, Baxter JD, Scanlan TS, Katzenellenbogen JA. Quantification of Ligand-Regulated Nuclear Receptor Corepressor and Coactivator Binding, Key Interactions Determining Ligand Potency and Efficacy for Thyroid Hormone Receptor. Biochemistry [Internet]. 2008 [cited 2018 Oct 8];47(28):7465–76. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2574600/pdf/nihms57470.pdf

Fig 1; An illustrative example of a comparison of cell lines is described in Figure 1, which shows that bar charts do not give the reader adequate information on the variability and distribution of each sampled '*n*'. This is because bar charts frequently do not adequately convey major features of the dataset. As explained below, Figure 1 illustrates why moving away from using bar charts to visualize the entire dataset is a necessary refinement that can increase the transparency and reporting of data.

" The extent of activation of a receptor in three cell lines a, b and c under baseline (drug-naïve) conditions and following the addition of a drug is given in arbitrary units. The same data sets are presented in three different ways: (A) bar chart, (B) grouped column scatter plot with means and error and (C) before–after scatter plot. *n* = 10 (i.e. biological replicates and not technical replicates). In this example, error bars represent the SEM although authors should consider the sampling size and distribution of '*n*' when choosing the most appropriate way of showing experimental error [e.g. SD or confidence interval]".



Appendix 1

Cell/molecular biological Goldilocks zones

- The level of the signal molecule mTOR which ensures proper functioning of the anti-tumour agent *Treg* in immune cells: Zeng (2017) –
- Appropriate proximity to the 'niche' environment in the crypt region of the colon in order to ensure the persistence of stem cell potential: Walther and Graham (2014)
- The need for microbial communities to be neither too distant nor too close for high levels of emergent biosynthetic capacity to occur (Chiu et al 2014)
- The need to maintain a balance in the expression, activation and repression of Pattern Recognition Receptors in order to promote immune system homeostasis in the GI tract: (Ringel-Scala et al 2016)
- An appropriate balance of the highly gene-dosage-sensitive Notch pathway, a fundamental signalling mechanism required for differentiation and tissue homeostasis; too much or too little can lead to disease. (Braune and Lendahl 2016)
- 'Goldilocks', is the name applied to the Python computer package which takes a census of gene sequence data to identify genomic regions which are 'just right' (Nicholls et al, 2013)
- Mechanoresponsive proteins have Goldilocks zones of actin binding affinity in order to carry out cytoskeleton reorganisation in response to changing mechanical environments. (Schiffhauer et al 2015)
- Understanding *Mycobacterium tuberculosis* infection requires information on the balance of key chemokines/cytokines and their receptors and how loss of that balance can promote disease (Domingo-Gonzalez et al 2016).
- The ideal 'Goldilocks' Chemistry allows DNA and RNA to carry out their fundamental function in molecular heredity (Houlihan et al 2017)
- An allosteric Serine- Arginine protein -phosphatase platform which balances phosphorylation levels in a 'goldilocks region' is required for the proper sub-nuclear stage of a protein kinase protein splicing factor (Aubot et al 2017)
- Methyl-CpG-binding protein (MeCP2) must stay within a narrow range of expression – not too much, not too little – to be functionally 'just right' for proper epigenetic regulation in order to limit devastating phenotypic outcomes (immune defects underlying neurological deficits) (Boothby and Williams, 2012)
- Undifferentiated Embryonic Cell Transcription Factor (Utf1) ensures that conditions are precisely right for maintaining pluripotency and self-renewal in embryonic stem cells (Laskowski and Knoepfler 2012)

Tissue/whole body biology applied in medicine Goldilocks zones

- To minimise the risk of bone fractures, vitamin D levels need to be between 'lower' and 'higher', both of which increase the risk (Baughman and Lower 2014)
- A high and low proportion of carbohydrate in the diet is associated with increased human mortality, with minimal risk at 50-55% carbohydrate intake (Seidelmann et al 2018)
- Appropriate redox balance in striated muscle, where ROS production is counterbalanced by antioxidant capacity requires a Goldilocks zone, which scales down from the whole tissue to mitochondrial level: Alleman et al 2014)
- Optimal development of advanced therapeutic medicinal products for bone repair need to be neither too simple nor too complex (Leijten et al 2015)
- Appropriate timing, dose and regimen of estrogen exposure is required to promote beneficial effects on cognition (Koenele and Bimonte-Nelson, 2015)
- Vitamin C concentrations which are 'just right' (especially not unphysiologically high) are needed in order to interpret effects of the vitamin on human physiology (Padayatty and Levine, 2016)
- Recommendations for post-polypectomy surveillance should aim to target a Goldilocks zone (Ladabaum and Schoen, 2016)
- The need to balance fetal needs vs maternal supply during pregnancy in great apes and humans in terms of the level of inflammation; is essential during implantation; otherwise there is the risk of disorders such as gestational diabetes and choriodecidual inflammatory syndrome (Clancy, 2013).
- With regard to fluid management around the time of surgery – too little (pre- and post- operatively) is associated with inadequate organ perfusion and too much, with tissue oedema and surgical complications. Finding the 'Goldilocksian' 'just right' zone is the challenge (Cuthbertson, 2013).
- Judicious surgery for breast cancer indicates that a 2mm margin is superior to a narrower one in patients with Ductal Carcinoma In Situ and that bigger is not necessarily better (Jagsi 2016)
- Networks of neurones need to stay in a Goldilocks zone between 'too quiet' and 'too active' (Humphries 2016).
- The 'Goldilocks zone' of fatty acid metabolism is required to ensure that the relationship with cardiac function is just right. (Kerr et al 2017).

- In emergency medicine a balance needs to be struck between the speed of treatment and its accuracy – sicker patients are more likely to benefit from intervention whereas less sick do not and may be harmed. It is necessary to get into the *Goldilocks zone*; the 'just right' balance between speed and accuracy (Fatovich, 2017)
- In the use of exercise to maintain joint homeostasis in the horse, too little or too much can result in joint derangement whereas just the right amount will provide optimal functioning of the joint (Milner 2017).
- In the treatment of perioperative blood pressure, the anaesthetist should aim at the 'Goldilocks' range, reminiscent of the optimal haemoglobin concentration, and avoid excursions in either direction (Sweitzer and Howell, 2017)
- 'Goldilocks' software is used in facilitating hearing-aid self-fitting *to allow user exploration and selection of preferred levels of overall output, low-frequency cut and high frequency boost*. (Boothroyd et al 2017).
- In the administration of oxygen in the clinical situation, the move is to avoid both excessive and inadequate therapy – moving away from the notion that more is always better and instead giving the least amount necessary (Martin and Grocott 2017).
- A 'Goldilocks trial design' constantly asks *'Is the sample size too big, too small or just right?*' As an example, Broglio et al (2014) present a Bayesian adaptive design for a confirmatory trial to select a trial's sample size based on accumulating data
- The Goldilocks dilemma in acute ischemic stroke asks which patients are 'just right' for endovascular treatments (Tansy and Liebeskind 2013)
- Excess or deficiency of retinoic acid leads to inner ear dysmorphogenesis via an effect on FGF3/1`1`2121FGF10 signalling; referred to as a Goldilocks phenomenon (Frenz et al 2010)
- For patients with newly diagnosed glioblastoma, the goal is to define the 'Goldilocks zone' for the optimal duration of adjuvant temozolomide (Grossman and Keleinberg 2017)
- Following lung injury, different progenitor cell populations can arise depending on the molecular environment – resulting in normal or aberrant alveolar repair. A key question is how to maintain a 'Goldilocks zone' of repair (Dean and Lloyd 2017) – nice diagram
- The design of inferior vena cava filters for the treatment of Venous thromboembolic disease relies on a 'Goldilocks' premise: i.e., make the device stable, (so it doesn't migrate) but not too stable (so you can still retrieve it) (Magnowski et al 2017)

- Genetic variation in humans occurs through different types of alleles; at one extreme are mutations that cause Mendelian disease such as familial hypercholesterolemia arising from mutations in the LDL receptor with powerful phenotypic effects; at the other are common alleles (eg. ApoE) with small phenotypic effects. In the middle are 'Goldilocks alleles' (e.g., PCSK9) where the mutations are common enough to be useful in epidemiological analyses (in contrast to Mendelian) but still produce detectable biochemical effects. (Cohen, 2013)
- Fetal androgen production, especially testosterone, needs to be 'just right' to ensure the appropriate developmental trajectory of the fetus and offspring, while inappropriate fetal androgen or androgen signalling – both too little and too much - is associated with disorders of male reproductive development as well as being implicated in Polycystic Ovarian Syndrome in women (Fowler and O'Shaughnessy 2013).

Human Behaviour Goldilocks zones

- Social auditory stimuli intermediate between 'predictable' and 'complex' best serve the selective attention of 7-8-month old infants: Kidd et al (2016)
- An optimal amount of social interactivity of television watching promotes children's visual attention and word learning (Nussenbaum and Amso, 2016).
- When considering the wellbeing of adolescents, 'too little' digital screen use may deprive them of important social information and peer pursuits whereas 'too much' may displace other meaningful activities (Przybylski and Weinstein 2017)

Human educational training needs Goldilocks zones

- The degree of specialisation required to ensure the acquisition of professional competences in Paediatric Psychological training (Steele et al 2014)

Healthcare

- The 'Goldilocks point' in Palliative Care refers to exactly the right time to mobilise specialist hospital/palliative care services for the patient sub-group who will derive the most benefit. (LeBlanc et al 2014)

- The Goldilocks Principle is invoked in the regulation of healthcare to make sure it is not too little, nor too much but 'just right': Kemple (2016)

- The need for Children's Health Insurance to provide 'just the right health outcomes, just the right patient care experience and just the right costs': Szilagyi (2015)

Zeng H. (2017) mTOR signalling in immune cells and its implications for cancer immunotherapy. Cancer Letters; 408: 182-189

Walther V, Graham TA (2014) Location, location, location! The reality of life for an intestinal stem cell in the crypt. J Pathol; 234: 1-4.

Chiu H-C, Levy R, Borenstein E (2014). Emergent biosynthetic capacity in simple microbial communities. PLOS Computational Biology; 10: e1003695

Ringel-Scala VM, McDaniel DK, Allen IC (2016) The Goldilocks Conundrum: NLR inflammasome modulation of gastrointestinal inflammation during inflammatory bowel disease. Crit Rev Immunol; 36: 283-314

Braune EB, Lendahl U (2016) Notch- a goldilocks signalling pathway in disease and cancer therapy. Discov Med; 115: 189-196

Nicholls SM, Clare A and Randall JC (2013) Goldilocks: a tool for identifying regions that are 'just right'. Bioinformatics; 32: 2047-2049

Schiffhauer ES, Luo T, Mohan K, Srivastava V, Qian X, Griffis, ER Iglesias PA, Robinson DN (2016) Mechanoaccumulative elements of the mammalian actin cytoskeleton. Curr Biol; 26: 1473-1479.

Domingo-Gonzalez R, Prince O, Cooper A, Khader SA (2016) Cytokines and chemokines in Mycobacterium tuberculosis infection. Microbiol Spectr; 4 doi 10.1128/microbiolospec. TBTB2-oo18-2016.

Houlihan G, Arangundy-Franklin S, Holliger P (2017). Exploring the chemistry of genetic information storage and propagation through polymerase engineering. Acc Chem Res; 50: 1079-1087

Aubot BE, Hailye KL, Fattet L, Jennings PA, Adams JA (2017) Redirecting SR protein nuclear trafficking through an allosteric platform. J Mol Biol; 429: 2178-2191

Boothby M, Williams GL (2012) The Goldilocks effect. Sci Transl Med.4:163fs42

Laskowski AI Knoepfler PS (2012) Utf1:Goldilocks for ES Bivalency. Cell Stem Cell 7:732-734

Baughman RP, Lower EE (2014) Goldilocks, vitamin D and sarcoidosis. Arthritis Res Ther 16: 111-113

Seidelmann SB, Claggett B, Cheng S, Henglin M, Shah A, Steffen LM, Folsom AR, Rimm EB, Willett Wc, Solomon SD (2018) Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. The Lancet on line August 16 2018 http://cix.doi.org/10.1016/S2468-2667 (18)30135-X

Alleman RJ, Katunge LA, Nelson MAM, Brown DA, Anderson EJ (2014). The 'Goldilocks Zone' from a redox perspective – Adaptive vs. deleterious responses to oxidative stress in striated muscle. Frontiers in Physiology; 5: 1-20.

Leijten J, Chair YC, Papantoniou I, Gens L, Schrooten J, Luyten FP (2015). Cell-based advanced therapeutic medicinal products for bone repair: Keep it simple? Advanced Drug Delivery Reviews 84: 30-44

Koebele SV, Bimonte-Nelson HA (2015). Trajectories and phenotypes with estrogen exposures across the lifespan: What does Goldilocks have to do with it? Horm Behav 74: 86-104

Padayatty SJ, Levine M (2016). Vitamin C physiology: the known and the unknown Goldilocks. Oral Dis 22: 463-493

Ladabaum U, Schoen RE (2016) Post-polypectoy surveillance that would please Goldilocks – not too much, not too little, but just right. Gastroenterology; 150: 791-796.

Clancy KBH (2007) Inflammation, Reproduction, and the Goldilocks Principle. In KBH Clancy, K Hinde, K and JN Rutherford: Building babies: primate development in proximate and ultimate perspective. Developments in Primatology 37,DOI 10.1007/978-1-4614-4060_1 Springer Science+Business Media New York, p4614-4060.

Cuthbertson BH (2013) Goldilocks, elephants and surgical fluids. Br J Anaesth;110, 144–145, https://doi.org/10.1093/***bja***/ ...

Jagsi R (2016) Goldilocks and margins for DCIS: identifying 'just right'. Practical radiation oncology 6: 296-297.

Humphries MD (2016) The Goldilocks zone in neural circuits. eLife 5: e22735

Kerr M, Dodd MS, Heather LC (2017) the 'Goldilocks zone' of fatty acid metabolism; to ensure that the relationship with cardiac function is just right. Clin Sci 131: 2079-2094.

Fatovich DM (2017). The time paradox of emergency medicine: another inverted U curve. Emerg Med Australas 29: 730-732.

Milner PI (2017) Keeping joints healthy: The Goldilocks effect of exercise. Veterinary Journal 226: 4-5.

Sweitzer BJ, Howell SJ (2017) The Goldilocks principle as it applies to perioperative blood pressure: what is too high, too low, or just right? Br J Anaesth 119: 7-10

Boothroyd A, Mackersie C (2017) A 'Goldilocks' approach to hearing-aid self-fitting: user interactions. Am J Audiol; 26: 430-435

Martin D, Grocott M (2017) Oxygen therapy and the Goldilocks principle. J Intensive Care Soc 18: 279-281

Broglio KR, Connor JT, Berry SM (2014) Not too big, not too small: a goldilocks approach to sample size selection 24: 685-705

Tansy AP, Liebeskind DS (2013). The goldilocks dilemma in acute ischemic stroke. Front Neurol 4: 164-166.

Frenz DA, Liu W, Cveki A, Xie Q, Wassef L, Loredana Q, Niederreither K, Maconochie, M Shanske A (2010) Retinoid signalling in inner ear development: a 'Goldilocks' phenomenon. Am J Med Genet A 152A: 2947-2961

Grossman SA, Kleinberg L (2017) A search for the 'Goldilocks zone' with regard to the optimal duration of adjuvant temozolomide in patients with glioblastoma. Neuro-Oncology 19: 1019-1020

Dean CH, Lloyd CM (2017) Lung alveolar repair: not all cells are equal. Trends Mol Med 23: 871-873.

Magnowski A, Brown M, Schramm K, Lindquist J, Rochun PJ, Johnson T (2017). The law of unintended consequences: current design challenges in inferior vena cava filters; Expert Rev Med Devices 14: 805-810

Cohen JC (2013) Emerging LDL therapies: using human genetics to discover new therapeutic targets for plasms lipids. J Clin Lipidol 7: S1-S5

Fowler PA, O'Shaughnessy PJ (2013). The Goldilocks principle and developmental androgens in males; what Is "just right"? Endocrinology 154: 1663-1671.

Kidd C, Piantadosi ST, Aslin RN (2014) The Goldilocks effect in infant auditory attention. Child Dev 85: 1795-1804

Nussenbaum K, Amso D (2016) An attentional Goldilocks effect: an optimal amount of social interactivity promotes word learning from video. J Cogn Dev 17: 30-40.

Przybylski A, Weinstein N (2017) A large-scale test of the Goldilocks hypothesis: quantifying the relations between digital-screen use and the mental well-being of adolescents. Psychol Sci 28: 204-215

Steele RG, Borner KB, Roberts MC (2014) Commentary: finding the middle bowl: Goldilocks' lessons on professional competences in pediatric psychology' J Pediat Psychol 39: 988-997

LeBlanc TW, Currow DC, Abernethy AP (2014) On Goldilocks, care coordination, and palliative care: making it 'just right'. Prim Care Respir J 23: 8-10

Kemple T (2016) The Goldilocks problems in regulation. BMJ 2016; 354:i3778

Szilagyi PG (2015) The children's'. health insurance program and the Goldilocks effect. Acad Pediatr 15: S13-S14

BMJ Open

Going to extremes: the Goldilocks/Lagom principle and data distribution

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-027767.R2
Article Type:	Communication
Date Submitted by the Author:	20-Aug-2019
Complete List of Authors:	Leese, Henry; University of Hull, Hull York Medical School Sathyapalan, Thozhukat; Hull Royal Infirmary, Diabetes and Endocrinology Allgar, Victoria; York University, HYMS/Health Sciences Brison, Daniel; Central Manchester University Hospitals NHS Foundation Trust, Department of Reproductive Medicine Sturmey, Roger; University of Hull, Hull York Medical School
Primary Subject Heading:	Medical publishing and peer review
Secondary Subject Heading:	Medical education and training, Research methods
Keywords:	STATISTICS & RESEARCH METHODS, Data analysis and interpretation, Data distributions

Going to extremes: the Goldilocks/Lagom principle and data distribution

Henry J Leese [1*], Thozhukat Sathyapalan [2,3], Victoria Allgar [4], Daniel R Brison [5,6] & Roger G Sturmey [1]

1, Centre for Atherothrombosis and Metabolism, Hull York Medical School, University of Hull, Hull, HU6 7RX, UK

2, Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, Hull, HU6 7RK UK

3, Department of Endocrinology, Hull and East Yorkshire Hospitals NHS Trust, Hull, UK

4, Hull York Medical School, University of York, York YO10 5DD, UK

5, Maternal and Fetal Health Research Centre, Division of Developmental Biology and Medicine, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Sciences Centre, St. Mary's Hospital, Manchester, M13 9WL, United Kingdom

6, Department of Reproductive Medicine, St. Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, M13 9WL, United Kingdom

* To whom correspondence should be addressed: henry.leese@hyms.ac.uk

Abstract

Numerical data in biology and medicine are commonly presented as mean or median with error or confidence limits, to the exclusion of individual values. Analysis of our own and others' data indicates that this practice risks excluding 'Goldilocks' effects in which a biological variable falls within a range between 'too much' and 'too little' with a region between where its function is 'just right'; a concept captured by the Swedish term 'Lagom'. This was confirmed by a narrative search of the literature using the PubMed Database, which revealed numerous relationships of biological and clinical phenomena of the Goldilocks/Lagom form including quantitative and qualitative examples from the health and social sciences. Some possible mechanisms underlying these phenomena are considered. We conclude that retrospective analysis of existing data will most likely reveal a vast number of such distributions to the benefit of medical understanding and clinical care and that a transparent approach of presenting each value within a data set individually should be adopted to ensure a more complete evaluation of research studies in future.

174 words

Going to extremes: the Goldilocks/Lagom principle and data distribution

Text

Introduction

Numerical data in science and medicine have traditionally been presented as mean or median values with standard errors or standard deviations. Such data commonly take the form of tables, bar graphs or line graphs. However, as (1) point out, this practice poses a problem since different distributions of data can lead to the same bar or line graph. This was well illustrated recently by (2) who used illustrative data from a hypothetical experiment to examine the impact of three different cell lines on drug receptor activation and showed that a variety of distributions of individual data points can lead to similar bar graphs with the same mean (Fig 1). This is because bar charts frequently do not convey major features of the dataset adequately. As Figure 1 makes clear, away from using bar charts to visualize the entire dataset is a necessary refinement that can increase the transparency and reporting of data.

" The extent of activation of a receptor in three cell lines a, b and c under baseline (drug-naïve) conditions and following the addition of a drug is given in arbitrary units. The same data sets are presented in three different ways: (A) bar chart, (B) grouped column scatter plot with means and error and (C) before–after scatter plot. *n* = 10 (i.e. biological replicates and not technical replicates). In this example, error bars represent the SEM although authors should consider the sampling size and distribution of '*n*' when choosing the most appropriate way of showing experimental error [e.g. SD or confidence interval]".

The attention paid to individual variation in cellular and molecular biological and clinical studies is relatively recent, but has been well-known for many years to ecologists, especially following the publication by Albert F. Bennett, in 1987, of an influential article entitled: *Inter-individual variability: an underutilized resource*'. Bennett, an ecological physiologist, pointed out that mean values with confidence intervals about the mean, once published tend to *'-- take on a life of their own, and become the only point of analysis and comparison'* to the exclusion of the individual values, and their potential significance. Bennett referred to this tendency as *'the tyranny of the Golden Mean',* and as an alternative, advocated the analysis of inter-individual variability, i.e., the full range of individual values, he considered could provide the observer with a greater interpretative repertoire.

In the time since Bennett's paper, there has been a movement away from the tyranny of the mean in many areas of biology, notably in ecology (3). Examples are provided by Stephen J Gould (4), who wrote an article on '*The median isn't the message'*, Hayes and Jenkins (5) on individual variation in mammals, and Lloyd-Smith (6) on the spread of epidemics of human disease.

Our interest in inter-individual variability arose particularly from research in which we have been involved on (a) the development and metabolism of single preimplantation mammalian embryos (DB, HL, RS) and (b) of glycaemic control in individual human subjects (TS).

(a) Development and metabolism of single preimplantation embryos

Data which illustrate the value of distributions rather than mean or median values were provided by (7) who measured the consumption of the essential nutrient, pyruvate, by single bovine preimplantation embryos at the zygote stage (1-cell fertilised egg; day 1 of development). The experiments revealed considerable heterogeneity between individual embryos such that it was possible to divide them prospectively into 3 groups - of 'high', 'intermediate' and 'low' pyruvate consumption at an early stage (day 2) - and track their subsequent development to the blastocyst stage, a critical developmental endpoint. These data indicated that intermediate values of pyruvate consumption correlated with viability (capacity to form a blastocyst), though with considerable overlap between the categories. Put another way, which takes account of this overlap, plotting individual values revealed the existence of an optimal 'range' of metabolic activity. This concept was developed in a follow-up paper (8) in which we proposed that the optimal range was equivalent to a 'Goldilocks zone' or as it is known in Sweden, of 'lagom', meaning 'just the right amount', in which embryos with maximum developmental potential are located.

(b) Glycaemic control

Glycated haemoglobin (HbA1c) is a marker of glycaemic control in patients with diabetes which is commonly used in clinical practice. Indeed, (HbA1c) is the recommended test for diagnosing diabetes. (9). There is an association between the extent of high blood glucose as measured by HbA_{1c} and the risk of death and of macrovascular and microvascular disease in patients with type 2 diabetes (T2DM) (10). In the landmark United Kingdom Prospective Diabetes Study, intensive glycaemic control that aimed to achieve a HbA_{1c} level of 7% or below was associated with improved outcome in newly diagnosed patients with type 2 diabetes (T2DM) (11). This finding was then extrapolated to all patients with T2DM, and as a result, lower HbA1c levels were recommended for management of patients with T2DM. However, concerns arose as data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial began to emerge showing increased all-cause mortality and cardiovascular mortality in the intensive treatment group who were treated with antihyperglycaemic agents aiming for a lower HbA_{1c} target of 6% compared with conventional antihyperglycaemic treatment in patients with T2DM aiming for HbA_{1c} of 7-7.9%. These results led to early termination of the trial (12). Further studies (13,14)have

demonstrated that lower and higher mean HbA1c values were associated with an increased risk of cardiovascular events and mortality suggesting a "Goldilocks' or 'lagom" state of HbA1c is the optimal.

Similar "U" shaped associations with HbA1c and all-cause mortality have also been shown for type 1 diabetes (15). Even in patients without diabetes, extremes of glycaemia as measured by HbA1c are associated with adverse clinical outcomes including cardiovascular events and all-cause mortality. Similar increases in mortality in either extremes are seen with body weight, blood pressure, birth weight, cholesterol and other cardiovascular risk factors.

Goldilocks and Lagom

The Goldilocks zone has been defined mathematically by (16) in the context of xenobiotic ligand binding to nuclear receptors as a *'Non-monotonic receptor-mediated dose-response curve'* (NMDRC), and by (17) in the context of endocrine disrupting chemicals as '*a response where the slope of the curve changes sign from positive to negative or vice versa somewhere along the range of doses examined*'. These are valuable definitions because they can be applied to all non-linear distributions including U-shaped, inverted U-shaped, J-shaped, sigmoidal and reverse sigmoidal.

The U-shaped curve is probably the most widely observed. It usually refers to the nonlinear relationship between two variables, in particular, a dependent and an independent variable. Because many analytical methods assume an underlying linear relationship, systematic deviation from linearity can lead to bias in estimation of safe levels in exposure to nutrients, drugs or toxic agents (for a discussion see section on *Mechanisms* below and (17)).

How widespread is the presence of a Goldilocks zone in biology and medicine?

We thought it might be instructive to discover how widely the notion of a 'Goldilocks zone' is a feature of the wider biological literature, especially as applied to medicine. A comprehensive search for information conducted on the *PubMed* database in early 2018 using the term 'Goldilocks' revealed 184 entries, all of which have been examined, together with the grey literature. Only articles in English language were selected. A selection of 43 of these publications has been presented (Appendix 1) as representative of the range of phenomena which invoke the Goldilocks concept in order to increase biological and clinical understanding. It should be emphasised that this is a narrative review rather than systematic review and no judgement on the quality of these studies or of those which have been omitted

is implied. Patient/public involvement: No members of the public, nor patients were involved in the synthesis of this manuscript.

Inspection of these examples reveals the wide range of biological and clinical phenomena in which Goldilocks zones have been found including the health and social sciences which can be qualitative rather than quantitative. It seems likely that a vast number remain to be discovered and that authors could, in a relatively simple manner, derive added value from their existing data by presenting distributions rather than median/mean values, and making raw data available to the research community via online repositories. This would allow systematic re-analysis by data scientists with an interest in the Goldilocks/Lagom concept.

Mechanisms underlying the Goldilocks Principle and what is Lagom

Mechanisms which are global in scope

We previously proposed an explanation that may account for Goldilocks/Lagom phenomena, derived from our work on energy efficiency in early mammalian embryo development (8) which made use of an account of general aspects of biological optimisation by (18). The premise was that living things aim to function with the minimum input of energy, i.e., with high energetic efficiency. To accomplish this will obviously require a threshold level of metabolic activity to ensure a given process proceeds in an optimum, yet efficient manner, while the upper limit will be set by the capacity to increase metabolism vs '*the energy parsimony in almost everything (*living things*) do*' (18). The Goldilocks/Lagom zone will obviously lie between these extremes. The boundaries will be set by homeostatic mechanisms at all levels of organisation. Such boundaries will be flexible in order to allow for the capacity to up- or down-regulate metabolism in response to stress. Responses of these types have been usefully categorised by ecologists to distinguish (a) modest changes in metabolism (up or down within the *optimum* (Goldilocks/Lagom) range) from which the cell/organism can recover (the so-called *Pejus* range) and (b) extreme perturbation beyond the optimum which shifts metabolism irreversibly into a *Pessimum* range which is fatal (see Fig 1 in the work of Sokolova (19)

Some *specific mechanisms* for the production of non-monotonic receptor-mediated dose-response curves (NMDRCs) were well summarised by (17) in terms of the effect of endocrine disrupting chemicals, notably Bisphenol A on cells in culture, whole organisms, laboratory animals and human populations. Interestingly, it was reported that NMDRCs were

common, comprising 20-30% of all studies examined, depending on the conditions; e.g., in vivo vs in vitro. Mechanisms considered included cytotoxicity (20), inhibition of cell proliferation (21); hormone receptors produced vs degraded (22); cell and tissue specific co-factors (23) and pharmacological effects. At the whole body level, examples of NMDRCs in nutrition are widespread, reflecting minimum requirments at the lower end of the distribution and toxicity at the higher, for example, vitamin A. Vandenberg (17) concludes that *'strong evidence for Non-monotonic receptor-mediated dose-response curves' - - question the current risk assessment practice where 'safe' levels are predicted from high dose exposures'*

Conclusion

There has long been a fixation in the biological and clinical research communities with presenting data solely as measures of dispersion (means and medians) and of central tendency (e.g., standard deviation and interquartile range). We believe that the retrospective analysis of existing data could reveal numerous potential relationships with a Goldilocks/Lagom pattern.

Interestingly, the editors of the British Journal of Pharmacology ' (2) '*will now require that, where possible, numerical data (whether categorical or continuous), particularly involving two sets or paired data, should be presented using scatter-plots, before-after graphs, and other forms in which each individual 'n' value is individually plotted, rather than using bar charts. Authors presenting data as bar charts should state that a scatter plot or before–after charts did not reveal unusual or interesting aspects of the data not obvious from the bar chart'.*

We believe the Journal should be complimented on this approach and urge all such journals to adopt it.

Author contributions:

H J Leese; conceived the study, conducted literature searches and wrote the first draft. All authors then commented on subsequent drafts. V Allgar; provided statistical advice, DR Brison; contributed to the initial concept and provided new material, as did RG Sturmey who also prepared the manuscript for submission T Sathyapalan; contributed to initial concept; provided new material and clinical expertise

Competing Interests:

The authors have no competing interests to declare in relation to this work.

Funding:
No specific funding was awarded for this research.

References

1. Weissgerber TL, Milic NM, Winham SJ, Garovic VD. Beyond Bar and Line Graphs: Time for a New Data Presentation Paradigm. PLoS Biol. 2015;13(4):1–10.
2. George CH, Stanford SC, Alexander S, Cirino G, Docherty JR, Giembycz MA, et al. Updating the guidelines for data transparency in the British Journal of Pharmacology - data sharing and the use of scatter plots instead of bar charts. Br J Pharmacol [Internet]. 2017 Sep 1 [cited 2018 Oct 4];174(17):2801–4. Available from: http://doi.wiley.com/10.1111/bph.13925
3. Roche DG, Careau V, Binning SA. Demystifying animal “personality” (or not): why individual variation matters to experimental biologists. J Exp Biol [Internet]. 2016 Dec 15 [cited 2018 Oct 4];219(Pt 24):3832–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27852750
4. Gould SJ. The Median Isn’t the Message [Internet]. [cited 2018 Oct 4]. Available from: https://people.umass.edu/biep540w/pdf/Stephen Jay Gould.pdf
5. Hayes JP, Jenkins SH. Individual Variation in Mammals. J Mammal [Internet]. 1997 May 21 [cited 2018 Oct 4];78(2):274–93. Available from: https://academic.oup.com/jmammal/article-lookup/doi/10.2307/1382882
6. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. Nature [Internet]. 2005 Nov 17 [cited 2018 Oct 4];438(7066):355–9. Available from: http://www.nature.com/articles/nature04153
7. Guerif F, McKeegan P, Leese HJ, Sturmey RG. A Simple Approach for COnsumption and RElease (CORE) Analysis of Metabolic Activity in Single Mammalian Embryos. PLoS One. 2013;8(8).
8. Leese HJ, Guerif F, Allgar V, Brison DR, Lundin K, Sturmey RG. Biological optimization, the Goldilocks principle, and how much is lagom in the preimplantation embryo. Mol Reprod Dev. 2016;83(9).
9. American Diabetes Association AD. Diagnosis and classification of diabetes mellitus. Diabetes Care [Internet]. 2011 Jan 1 [cited 2018 Oct 4];34 Suppl 1(Supplement 1):S62-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21193628
10. Khaw K-T, Wareham N. Glycated hemoglobin as a marker of cardiovascular risk. Curr Opin Lipidol [Internet]. 2006 Dec [cited 2018 Oct 4];17(6):637–43. Available from: https://insights.ovid.com/crossref?an=00041433-200612000-00006
11. Intensive blood-glucose control with sulphonylureas or insulin compared with

conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet [Internet]. 1998 Sep 12 [cited 2018 Oct 4];352(9131):837–53. Available from: https://www.sciencedirect.com/science/article/pii/S0140673698070196?via%3Dihub

12. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. N Engl J Med [Internet]. 2009 Jan 8 [cited 2018 Oct 4];360(2):129–39. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa0808431

13. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. Lancet. 2010;375(9713):481–9.

14. Forbes A, Murrells T, Mulnier H, Sinclair AJ. Mean HbA 1c , HbA 1c variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. Lancet Diabetes Endocrinol [Internet]. 2018;6(6):476–86. Available from: http://dx.doi.org/10.1016/S2213-8587(18)30048-2

15. Schoenaker DAJM, Simon D, Chaturvedi N, Fuller JH, Soedamah-Muthu SS. Glycemic Control and All-Cause Mortality Risk in Type 1 Diabetes Patients: The EURODIAB Prospective Complications Study. J Clin Endocrinol Metab [Internet]. 2014 Mar 1 [cited 2018 Oct 4];99(3):800–7. Available from: https://academic.oup.com/jcem/article-lookup/doi/10.1210/jc.2013-2824

16. Kohn MC, Melnick RL. Biochemical origins of the non-monotonic receptor-mediated dose-response [Internet]. Vol. 29, Journal of Molecular Endocrinology. 2002 [cited 2018 Oct 4]. Available from: http://www.endocrinology.org

17. Vandenberg LN. Non-monotonic dose responses in studies of endocrine disrupting chemicals: bisphenol a as a case study. Dose Response [Internet]. 2014 May [cited 2018 Oct 4];12(2):259–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24910584

18. Johnson AT. Teaching the principle of biological optimization. J Biol Eng [Internet]. 2013 Feb 20 [cited 2018 Oct 4];7(1):6. Available from: http://jbioleng.biomedcentral.com/articles/10.1186/1754-1611-7-6

19. Sokolova IM. Energy-Limited Tolerance to Stress as a Conceptual Framework to Integrate the Effects of Multiple Stressors. Integr Comp Biol [Internet]. 2013 Oct 1 [cited 2018 Oct 4];53(4):597–608. Available from: https://academic.oup.com/icb/article-lookup/doi/10.1093/icb/ict028

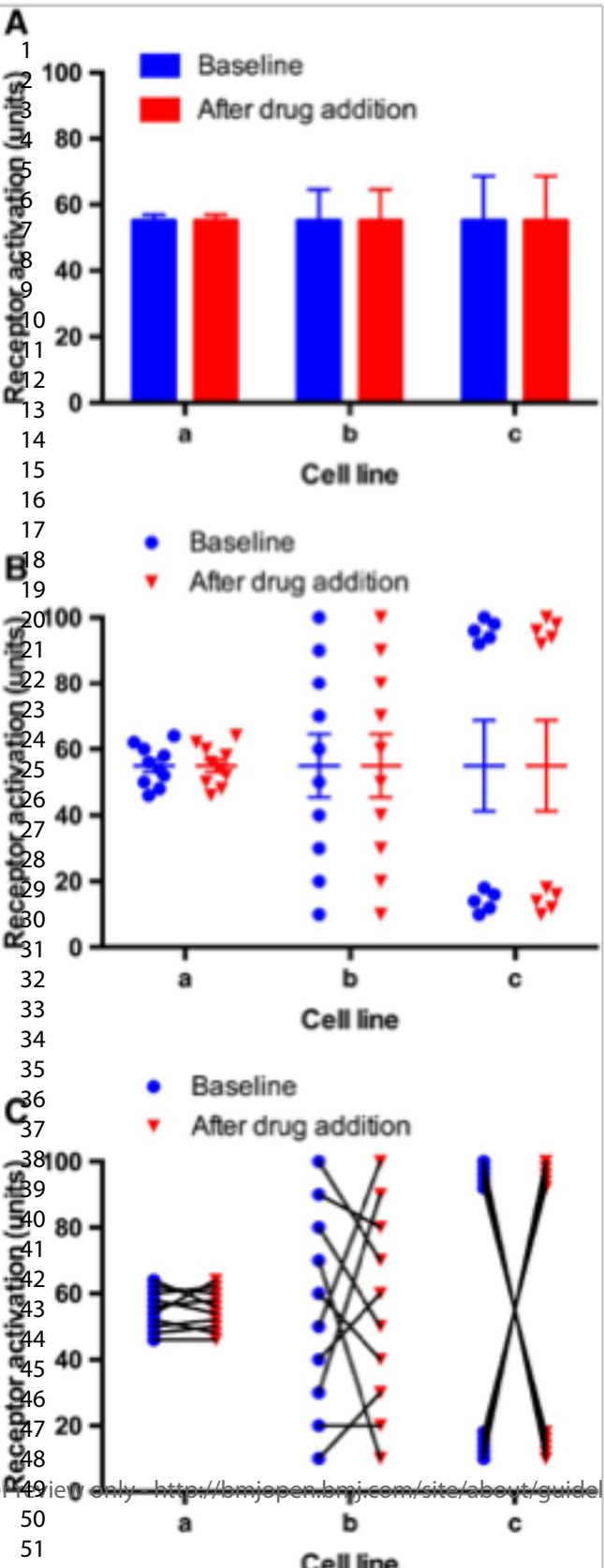
20. Welshons W V, Thayer KA, Judy BM, Taylor JA, Curran EM, Vom Saal FS. Large Effects from Small Exposures. I. Mechanisms for Endocrine-Disrupting Chemicals with Estrogenic Activity. 2003 [cited 2018 Oct 8];111. Available from: http://dx.doi.org/

21. SOTO AM, SONNENSCHEIN C, PRECHTL N, WEILL B, OLEA N. Methods to Screen Estrogen-Agonists and Antagonists. J Med Food [Internet]. 1999 Jan [cited 2018 Oct 8];2(3–4):139–42. Available from: http://www.liebertpub.com/doi/10.1089/jmf.1999.2.139

22. Ismail A, Nawaz Z. Nuclear hormone receptor degradation and gene transcription: An update. IUBMB Life (International Union Biochem Mol Biol Life) [Internet]. 2005 Jul 1 [cited 2018 Oct 8];57(7):483–90. Available from: http://doi.wiley.com/10.1080/15216540500147163

23. Jeyakumar M, Webb P, Baxter JD, Scanlan TS, Katzenellenbogen JA. Quantification of Ligand-Regulated Nuclear Receptor Corepressor and Coactivator Binding, Key Interactions Determining Ligand Potency and Efficacy for Thyroid Hormone Receptor. Biochemistry [Internet]. 2008 [cited 2018 Oct 8];47(28):7465–76. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2574600/pdf/nihms57470.pdf

Fig 1; An illustrative example of a comparison of cell lines is described in Figure 1, which shows that bar charts do not give the reader adequate information on the variability and distribution of each sampled '*n*'.



Appendix 1

Cell/molecular biological Goldilocks zones

- The level of the signal molecule mTOR which ensures proper functioning of the anti-tumour agent *Treg* in immune cells: Zeng (2017) –
- Appropriate proximity to the 'niche' environment in the crypt region of the colon in order to ensure the persistence of stem cell potential: Walther and Graham (2014)
- The need for microbial communities to be neither too distant nor too close for high levels of emergent biosynthetic capacity to occur (Chiu et al 2014)
- The need to maintain a balance in the expression, activation and repression of Pattern Recognition Receptors in order to promote immune system homeostasis in the GI tract: (Ringel-Scala et al 2016)
- An appropriate balance of the highly gene-dosage-sensitive Notch pathway, a fundamental signalling mechanism required for differentiation and tissue homeostasis; too much or too little can lead to disease. (Braune and Lendahl 2016)
- 'Goldilocks', is the name applied to the Python computer package which takes a census of gene sequence data to identify genomic regions which are 'just right' (Nicholls et al, 2013)
- Mechanoresponsive proteins have Goldilocks zones of actin binding affinity in order to carry out cytoskeleton reorganisation in response to changing mechanical environments. (Schiffhauer et al 2015)
- Understanding *Mycobacterium tuberculosis* infection requires information on the balance of key chemokines/cytokines and their receptors and how loss of that balance can promote disease (Domingo-Gonzalez et al 2016).
- The ideal 'Goldilocks' Chemistry allows DNA and RNA to carry out their fundamental function in molecular heredity (Houlihan et al 2017)
- An allosteric Serine- Arginine protein -phosphatase platform which balances phosphorylation levels in a 'goldilocks region' is required for the proper sub-nuclear stage of a protein kinase protein splicing factor (Aubot et al 2017)
- Methyl-CpG-binding protein (MeCP2) must stay within a narrow range of expression – not too much, not too little – to be functionally 'just right' for proper epigenetic regulation in order to limit devastating phenotypic outcomes (immune defects underlying neurological deficits) (Boothby and Williams, 2012)
- Undifferentiated Embryonic Cell Transcription Factor (Utf1) ensures that conditions are precisely right for maintaining pluripotency and self-renewal in embryonic stem cells (Laskowski and Knoepfler 2012)

Tissue/whole body biology applied in medicine Goldilocks zones

- To minimise the risk of bone fractures, vitamin D levels need to be between 'lower' and 'higher', both of which increase the risk (Baughman and Lower 2014)
- A high and low proportion of carbohydrate in the diet is associated with increased human mortality, with minimal risk at 50-55% carbohydrate intake (Seidelmann et al 2018)
- Appropriate redox balance in striated muscle, where ROS production is counterbalanced by antioxidant capacity requires a Goldilocks zone, which scales down from the whole tissue to mitochondrial level: Alleman et al 2014)
- Optimal development of advanced therapeutic medicinal products for bone repair need to be neither too simple nor too complex (Leijten et al 2015)
- Appropriate timing, dose and regimen of estrogen exposure is required to promote beneficial effects on cognition (Koenele and Bimonte-Nelson, 2015)
- Vitamin C concentrations which are 'just right' (especially not unphysiologically high) are needed in order to interpret effects of the vitamin on human physiology (Padayatty and Levine, 2016)
- Recommendations for post-polypectomy surveillance should aim to target a Goldilocks zone (Ladabaum and Schoen, 2016)
- The need to balance fetal needs vs maternal supply during pregnancy in great apes and humans in terms of the level of inflammation; is essential during implantation; otherwise there is the risk of disorders such as gestational diabetes and choriodecidual inflammatory syndrome (Clancy, 2013).
- With regard to fluid management around the time of surgery – too little (pre- and post- operatively) is associated with inadequate organ perfusion and too much, with tissue oedema and surgical complications. Finding the 'Goldilocksian' 'just right' zone is the challenge (Cuthbertson, 2013).
- Judicious surgery for breast cancer indicates that a 2mm margin is superior to a narrower one in patients with Ductal Carcinoma In Situ and that bigger is not necessarily better (Jagsi 2016)
- Networks of neurones need to stay in a Goldilocks zone between 'too quiet' and 'too active' (Humphries 2016).
- The 'Goldilocks zone' of fatty acid metabolism is required to ensure that the relationship with cardiac function is just right. (Kerr et al 2017).

- In emergency medicine a balance needs to be struck between the speed of treatment and its accuracy – sicker patients are more likely to benefit from intervention whereas less sick do not and may be harmed. It is necessary to get into the *Goldilocks zone*; the 'just right' balance between speed and accuracy (Fatovich, 2017)
- In the use of exercise to maintain joint homeostasis in the horse, too little or too much can result in joint derangement whereas just the right amount will provide optimal functioning of the joint (Milner 2017).
- In the treatment of perioperative blood pressure, the anaesthetist should aim at the 'Goldilocks' range, reminiscent of the optimal haemoglobin concentration, and avoid excursions in either direction (Sweitzer and Howell, 2017)
- 'Goldilocks' software is used in facilitating hearing-aid self-fitting *to allow user exploration and selection of preferred levels of overall output, low-frequency cut and high frequency boost*. (Boothroyd et al 2017).
- In the administration of oxygen in the clinical situation, the move is to avoid both excessive and inadequate therapy – moving away from the notion that more is always better and instead giving the least amount necessary (Martin and Grocott 2017).
- A 'Goldilocks trial design' constantly asks *'Is the sample size too big, too small or just right?*' As an example, Broglio et al (2014) present a Bayesian adaptive design for a confirmatory trial to select a trial's sample size based on accumulating data
- The Goldilocks dilemma in acute ischemic stroke asks which patients are 'just right' for endovascular treatments (Tansy and Liebeskind 2013)
- Excess or deficiency of retinoic acid leads to inner ear dysmorphogenesis via an effect on FGF3/1`1`2121FGF10 signalling; referred to as a Goldilocks phenomenon (Frenz et al 2010)
- For patients with newly diagnosed glioblastoma, the goal is to define the 'Goldilocks zone' for the optimal duration of adjuvant temozolomide (Grossman and Keleinberg 2017)
- Following lung injury, different progenitor cell populations can arise depending on the molecular environment – resulting in normal or aberrant alveolar repair. A key question is how to maintain a 'Goldilocks zone' of repair (Dean and Lloyd 2017) – nice diagram
- The design of inferior vena cava filters for the treatment of Venous thromboembolic disease relies on a 'Goldilocks' premise: i.e., make the device stable, (so it doesn't migrate) but not too stable (so you can still retrieve it) (Magnowski et al 2017)

- Genetic variation in humans occurs through different types of alleles; at one extreme are mutations that cause Mendelian disease such as familial hypercholesterolemia arising from mutations in the LDL receptor with powerful phenotypic effects; at the other are common alleles (eg. ApoE) with small phenotypic effects. In the middle are 'Goldilocks alleles' (e.g., PCSK9) where the mutations are common enough to be useful in epidemiological analyses (in contrast to Mendelian) but still produce detectable biochemical effects. (Cohen, 2013)
- Fetal androgen production, especially testosterone, needs to be 'just right' to ensure the appropriate developmental trajectory of the fetus and offspring, while inappropriate fetal androgen or androgen signalling – both too little and too much - is associated with disorders of male reproductive development as well as being implicated in Polycystic Ovarian Syndrome in women (Fowler and O'Shaughnessy 2013).

Human Behaviour Goldilocks zones

- Social auditory stimuli intermediate between 'predictable' and 'complex' best serve the selective attention of 7-8-month old infants: Kidd et al (2016)
- An optimal amount of social interactivity of television watching promotes children's visual attention and word learning (Nussenbaum and Amso, 2016).
- When considering the wellbeing of adolescents, 'too little' digital screen use may deprive them of important social information and peer pursuits whereas 'too much' may displace other meaningful activities (Przybylski and Weinstein 2017)

Human educational training needs Goldilocks zones

- The degree of specialisation required to ensure the acquisition of professional competences in Paediatric Psychological training (Steele et al 2014)

Healthcare

- The 'Goldilocks point' in Palliative Care refers to exactly the right time to mobilise specialist hospital/palliative care services for the patient sub-group who will derive the most benefit. (LeBlanc et al 2014)

- The Goldilocks Principle is invoked in the regulation of healthcare to make sure it is not too little, nor too much but 'just right': Kemple (2016)

- The need for Children's Health Insurance to provide 'just the right health outcomes, just the right patient care experience and just the right costs': Szilagyi (2015)

Zeng H. (2017) mTOR signalling in immune cells and its implications for cancer immunotherapy. Cancer Letters; 408: 182-189

Walther V, Graham TA (2014) Location, location, location! The reality of life for an intestinal stem cell in the crypt. J Pathol; 234: 1-4.

Chiu H-C, Levy R, Borenstein E (2014). Emergent biosynthetic capacity in simple microbial communities. PLOS Computational Biology; 10: e1003695

Ringel-Scala VM, McDaniel DK, Allen IC (2016) The Goldilocks Conundrum: NLR inflammasome modulation of gastrointestinal inflammation during inflammatory bowel disease. Crit Rev Immunol; 36: 283-314

Braune EB, Lendahl U (2016) Notch- a goldilocks signalling pathway in disease and cancer therapy. Discov Med; 115: 189-196

Nicholls SM, Clare A and Randall JC (2013) Goldilocks: a tool for identifying regions that are 'just right'. Bioinformatics; 32: 2047-2049

Schiffhauer ES, Luo T, Mohan K, Srivastava V, Qian X, Griffis, ER Iglesias PA, Robinson DN (2016) Mechanoaccumulative elements of the mammalian actin cytoskeleton. Curr Biol; 26: 1473-1479.

Domingo-Gonzalez R, Prince O, Cooper A, Khader SA (2016) Cytokines and chemokines in Mycobacterium tuberculosis infection. Microbiol Spectr; 4 doi 10.1128/microbiolospec. TBTB2-oo18-2016.

Houlihan G, Arangundy-Franklin S, Holliger P (2017). Exploring the chemistry of genetic information storage and propagation through polymerase engineering. Acc Chem Res; 50: 1079-1087

Aubot BE, Hailye KL, Fattet L, Jennings PA, Adams JA (2017) Redirecting SR protein nuclear trafficking through an allosteric platform. J Mol Biol; 429: 2178-2191

Boothby M, Williams GL (2012) The Goldilocks effect. Sci Transl Med.4:163fs42

Laskowski AI Knoepfler PS (2012) Utf1:Goldilocks for ES Bivalency. Cell Stem Cell 7:732-734

Baughman RP, Lower EE (2014) Goldilocks, vitamin D and sarcoidosis. Arthritis Res Ther 16: 111-113

Seidelmann SB, Claggett B, Cheng S, Henglin M, Shah A, Steffen LM, Folsom AR, Rimm EB, Willett Wc, Solomon SD (2018) Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. The Lancet on line August 16 2018 http://cix.doi.org/10.1016/S2468-2667 (18)30135-X

Alleman RJ, Katunge LA, Nelson MAM, Brown DA, Anderson EJ (2014). The 'Goldilocks Zone' from a redox perspective – Adaptive vs. deleterious responses to oxidative stress in striated muscle. Frontiers in Physiology; 5: 1-20.

Leijten J, Chair YC, Papantoniou I, Gens L, Schrooten J, Luyten FP (2015). Cell-based advanced therapeutic medicinal products for bone repair: Keep it simple? Advanced Drug Delivery Reviews 84: 30-44

Koebele SV, Bimonte-Nelson HA (2015). Trajectories and phenotypes with estrogen exposures across the lifespan: What does Goldilocks have to do with it? Horm Behav 74: 86-104

Padayatty SJ, Levine M (2016). Vitamin C physiology: the known and the unknown Goldilocks. Oral Dis 22: 463-493

Ladabaum U, Schoen RE (2016) Post-polypectoy surveillance that would please Goldilocks – not too much, not too little, but just right. Gastroenterology; 150: 791-796.

Clancy KBH (2007) Inflammation, Reproduction, and the Goldilocks Principle. In KBH Clancy, K Hinde, K and JN Rutherford: Building babies: primate development in proximate and ultimate perspective. Developments in Primatology 37,DOI 10.1007/978-1-4614-4060_1 Springer Science+Business Media New York, p4614-4060.

Cuthbertson BH (2013) Goldilocks, elephants and surgical fluids. Br J Anaesth;110, 144–145, https://doi.org/10.1093/***bja***/ ...

Jagsi R (2016) Goldilocks and margins for DCIS: identifying 'just right'. Practical radiation oncology 6: 296-297.

Humphries MD (2016) The Goldilocks zone in neural circuits. eLife 5: e22735

Kerr M, Dodd MS, Heather LC (2017) the 'Goldilocks zone' of fatty acid metabolism; to ensure that the relationship with cardiac function is just right. Clin Sci 131: 2079-2094.

Fatovich DM (2017). The time paradox of emergency medicine: another inverted U curve. Emerg Med Australas 29: 730-732.

Milner PI (2017) Keeping joints healthy: The Goldilocks effect of exercise. Veterinary Journal 226: 4-5.

Sweitzer BJ, Howell SJ (2017) The Goldilocks principle as it applies to perioperative blood pressure: what is too high, too low, or just right? Br J Anaesth 119: 7-10

Boothroyd A, Mackersie C (2017) A 'Goldilocks' approach to hearing-aid self-fitting: user interactions. Am J Audiol; 26: 430-435

Martin D, Grocott M (2017) Oxygen therapy and the Goldilocks principle. J Intensive Care Soc 18: 279-281

Broglio KR, Connor JT, Berry SM (2014) Not too big, not too small: a goldilocks approach to sample size selection 24: 685-705

Tansy AP, Liebeskind DS (2013). The goldilocks dilemma in acute ischemic stroke. Front Neurol 4: 164-166.

Frenz DA, Liu W, Cveki A, Xie Q, Wassef L, Loredana Q, Niederreither K, Maconochie, M Shanske A (2010) Retinoid signalling in inner ear development: a 'Goldilocks' phenomenon. Am J Med Genet A 152A: 2947-2961

Grossman SA, Kleinberg L (2017) A search for the 'Goldilocks zone' with regard to the optimal duration of adjuvant temozolomide in patients with glioblastoma. Neuro-Oncology 19: 1019-1020

Dean CH, Lloyd CM (2017) Lung alveolar repair: not all cells are equal. Trends Mol Med 23: 871-873.

Magnowski A, Brown M, Schramm K, Lindquist J, Rochun PJ, Johnson T (2017). The law of unintended consequences: current design challenges in inferior vena cava filters; Expert Rev Med Devices 14: 805-810

Cohen JC (2013) Emerging LDL therapies: using human genetics to discover new therapeutic targets for plasms lipids. J Clin Lipidol 7: S1-S5

Fowler PA, O'Shaughnessy PJ (2013). The Goldilocks principle and developmental androgens in males; what Is "just right"? Endocrinology 154: 1663-1671.

Kidd C, Piantadosi ST, Aslin RN (2014) The Goldilocks effect in infant auditory attention. Child Dev 85: 1795-1804

Nussenbaum K, Amso D (2016) An attentional Goldilocks effect: an optimal amount of social interactivity promotes word learning from video. J Cogn Dev 17: 30-40.

Przybylski A, Weinstein N (2017) A large-scale test of the Goldilocks hypothesis: quantifying the relations between digital-screen use and the mental well-being of adolescents. Psychol Sci 28: 204-215

Steele RG, Borner KB, Roberts MC (2014) Commentary: finding the middle bowl: Goldilocks' lessons on professional competences in pediatric psychology' J Pediat Psychol 39: 988-997

LeBlanc TW, Currow DC, Abernethy AP (2014) On Goldilocks, care coordination, and palliative care: making it 'just right'. Prim Care Respir J 23: 8-10

Kemple T (2016) The Goldilocks problems in regulation. BMJ 2016; 354:i3778

Szilagyi PG (2015) The children's'. health insurance program and the Goldilocks effect. Acad Pediatr 15: S13-S14