Lactobacillus johnsonii attenuates ovarian aging by remodeling the gut-ovary axis

Jiamin He[1,2#], Qiwen Wang[2,3#], Luyi Chen[1,2#], Yadong Qi[2,3#], Dingjiacheng Jia[3], Jilei Xu[1,2], Qingyi Wang[1,2], Yao Jiang[2,3], Jian Zhou[1,2], Yong Sun[2,3], Ruochen Yan[1,2], Lan Wang[1,2], Tongyao Hou[1,2], Zheng Kuang[4], Min Jin[3*], Liangjing Wang[2,3*], Shujie Chen[1,2*]

1 Sir Run Run Shaw Hospital of Zhejiang University School of Medicine
2 Prevention and Treatment Research Center for Senescent Disease of Zhejiang University School of Medicine
3 The Second Affiliated Hospital of Zhejiang University School of Medicine
4 Carnegie Mellon University

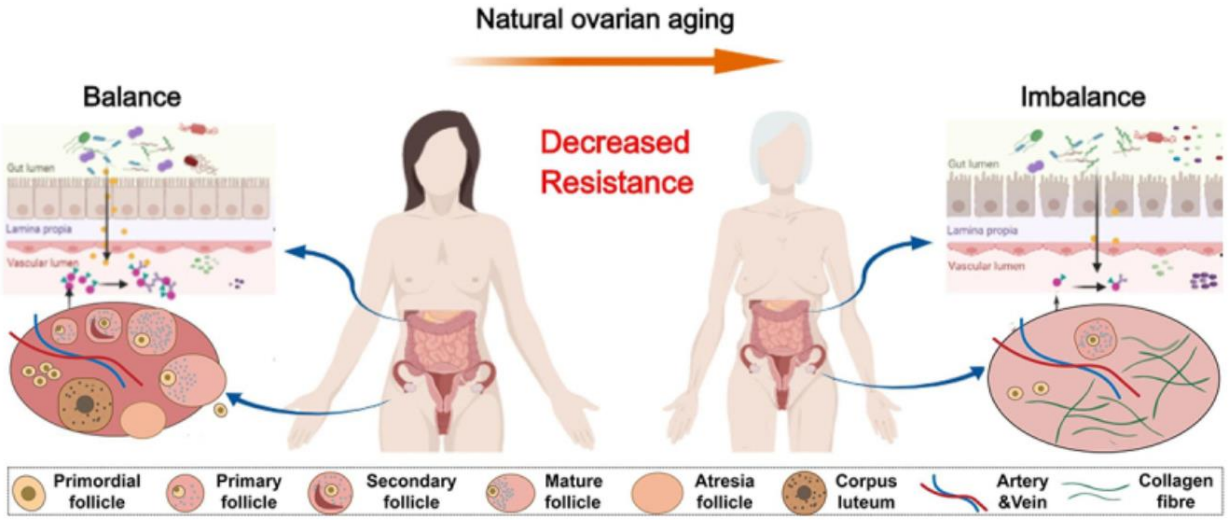


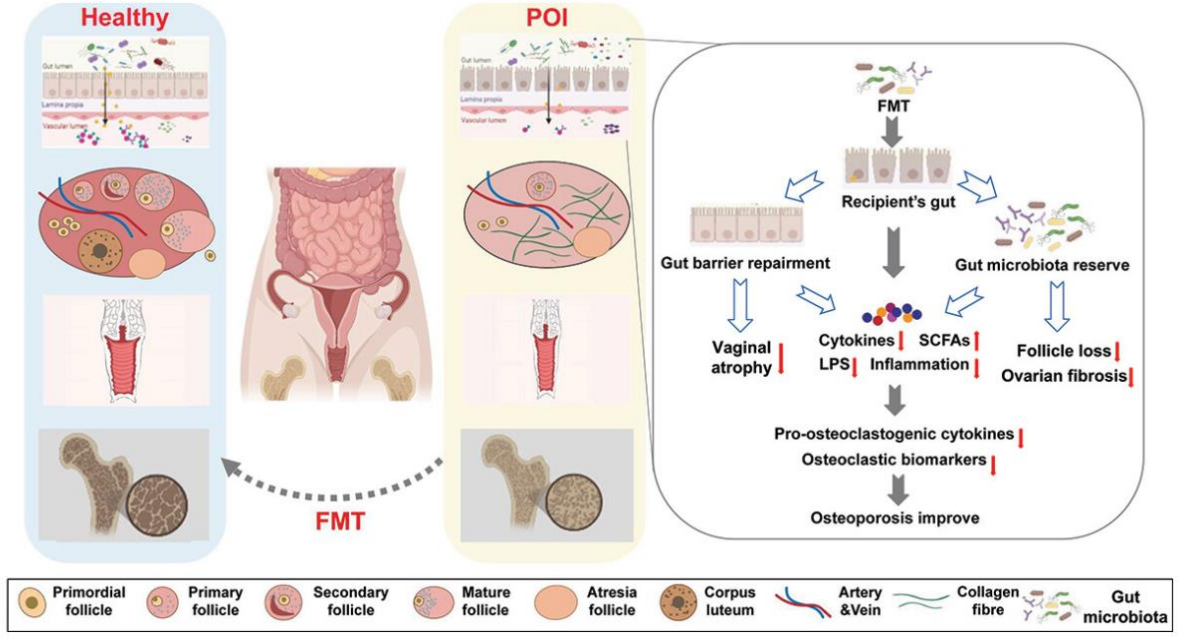
Jiamin He, Qiwen Wang, Luyi Chen, Yadong Qi, Dingjiacheng Jia, Jilei Xu, Qingyi Wang, et al. 2026. *Lactobacillus johnsonii* attenuates ovarian aging by remodeling the gut-ovary axis. ***iMetaOmics*** 3: e70152. https://doi.org/10.1002/imo2.70152

Clinical Challenges and Core Scientific Questions

Clinical landscape: Ovarian aging is accompanied by declining fertility, dysregulated bone metabolism, elevated cardiovascular risk, and cognitive impairment. Long-term hormone replacement therapy (HRT), the current mainstay, suffers from poor adherence, underscoring the urgent need for convenient, novel intervention strategies.

Knowledge gap： Gut microbiota has been established as a key regulator of systemic host aging; however, whether it governs ovarian function through the gut–ovary axis—and the identity of the core effector strain and its precise molecular mechanism—remain unresolved.





Gut Microbes 2024

L. johnsonii improves ovarian function in aging female mice

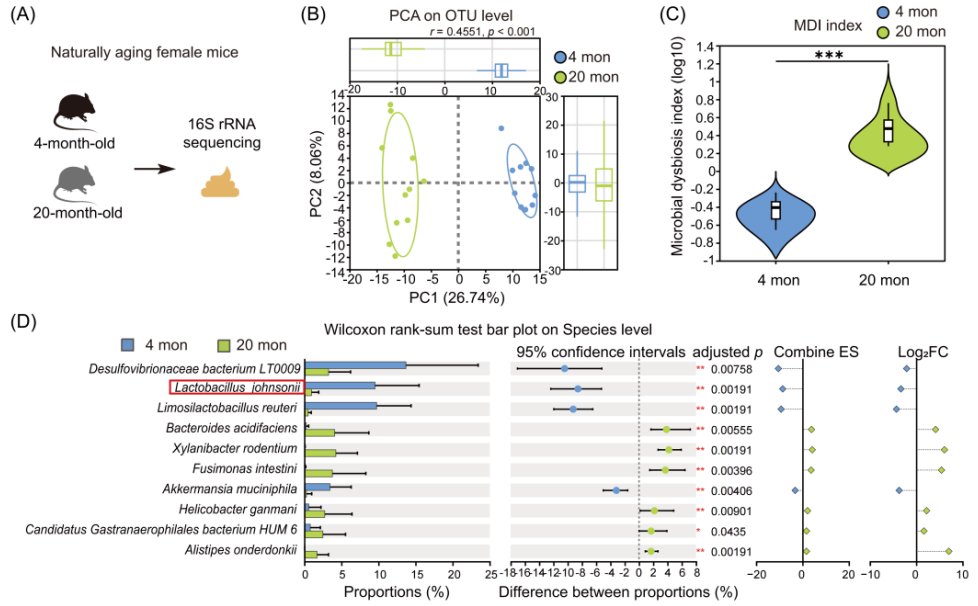
Key findings

Dysbiosis: 20-month-old mice show elevated MDI and reduced *L. johnsonii* vs. 4-month-old mice.

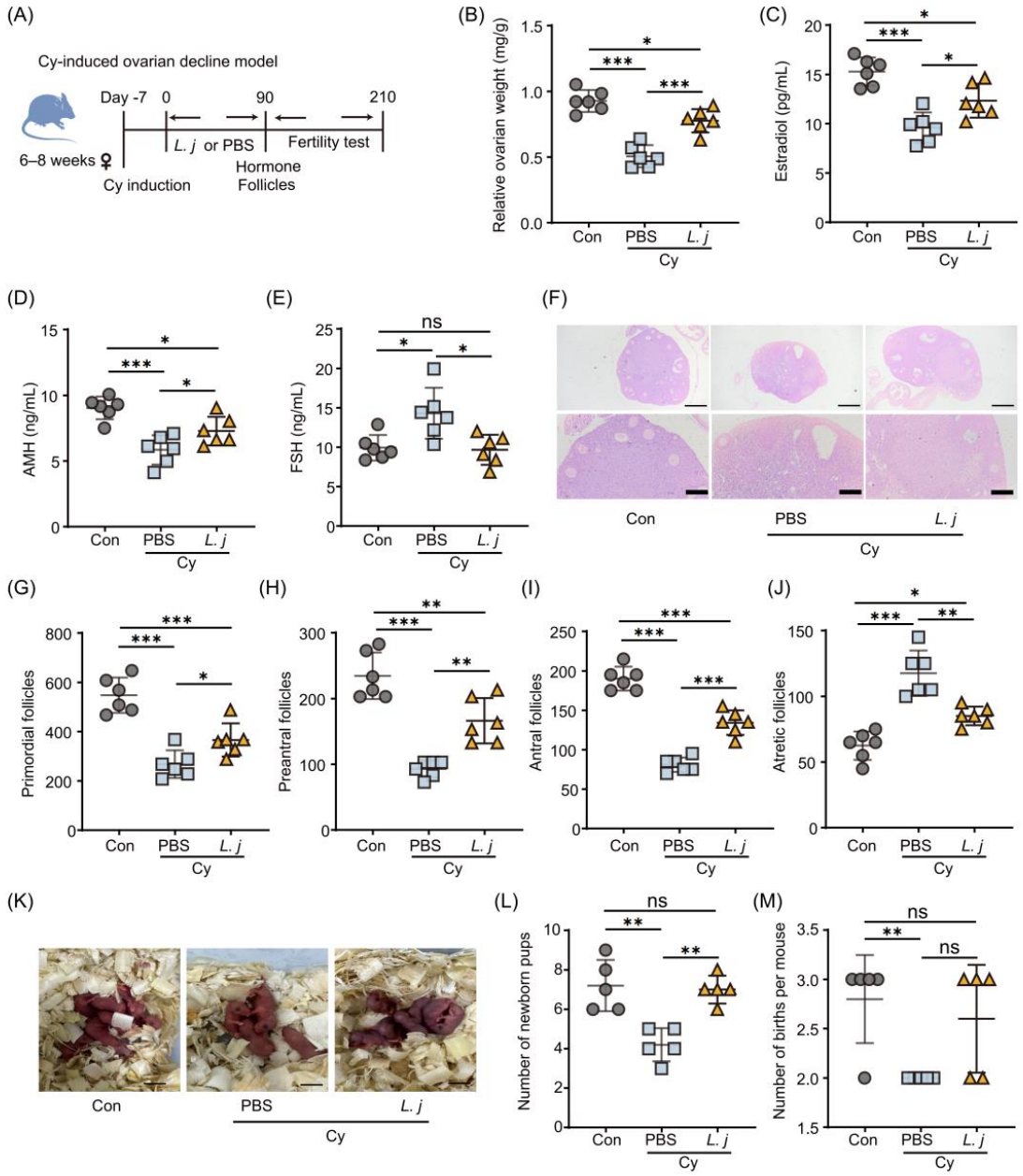
Ovarian improvement: 10-month gavage raises ovarian weight and plasma E2, lowers FSH; increases preantral/antral follicles and reduces atretic follicles.

Lifespan: Median survival of *Zmpste24*$^{-/-}$ progeroid females extended by **12.09%**; qPCR confirmed intestinal colonization.

No E2 rise in OVX mice → protection depends on direct ovarian regulation.



L. johnsonii improves ovarian function and fertilityin Cy-induced ovarian decline mice



Key findings

Hormone recovery: Cy-model elevates FSH and lowers E2/AMH; *L. johnsonii* reverses all three.

Follicle reserve: Primordial, preantral and antral follicle loss is rescued; atretic follicles reduced.

Fertility: First-litter pup count is significantly restored vs. Cy-model; long-term birth frequency trends upward.

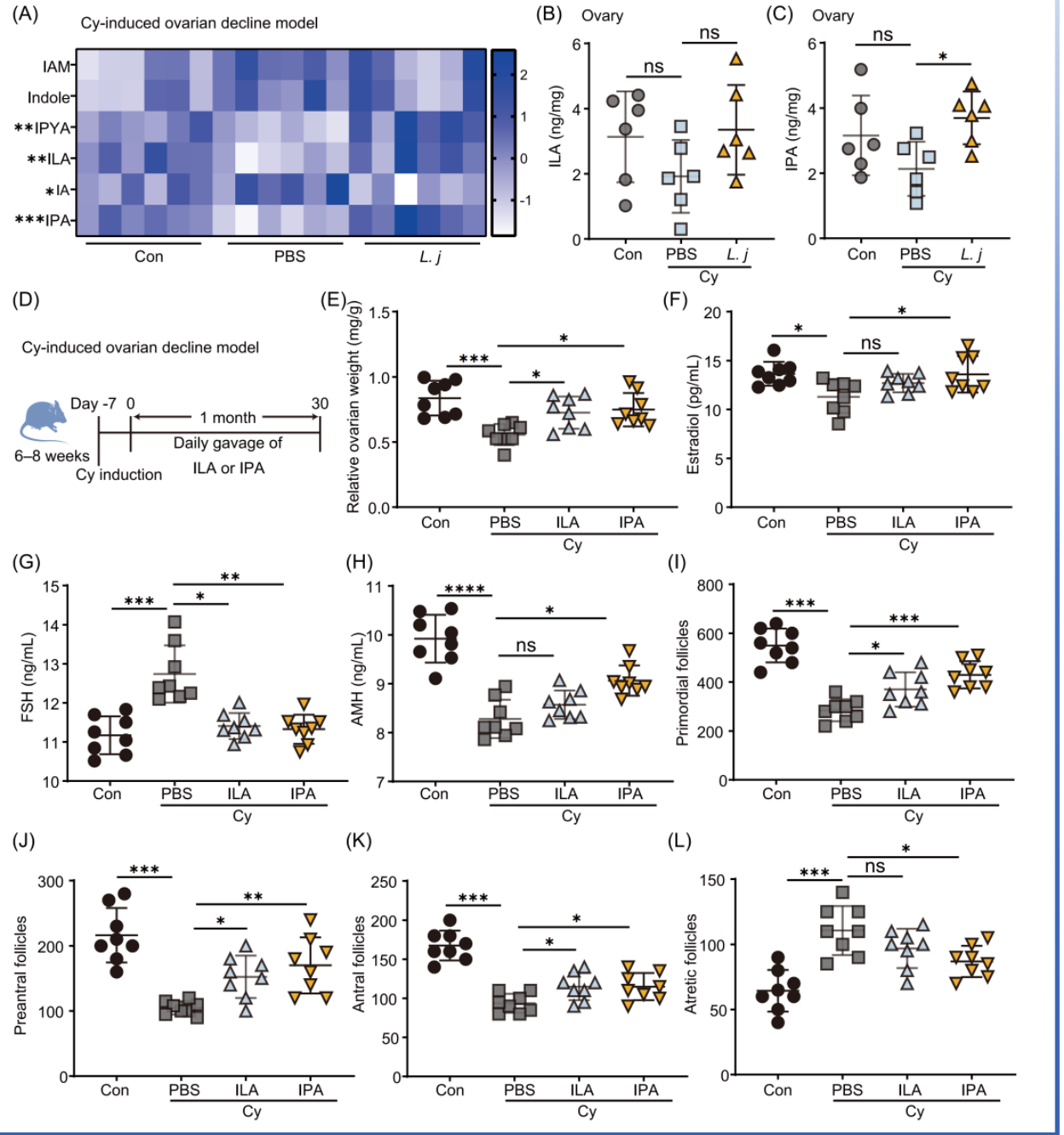
Microbiota-derived ILA and IPA improve ovarian function in Cy-induced ovarian decline mice

Key findings

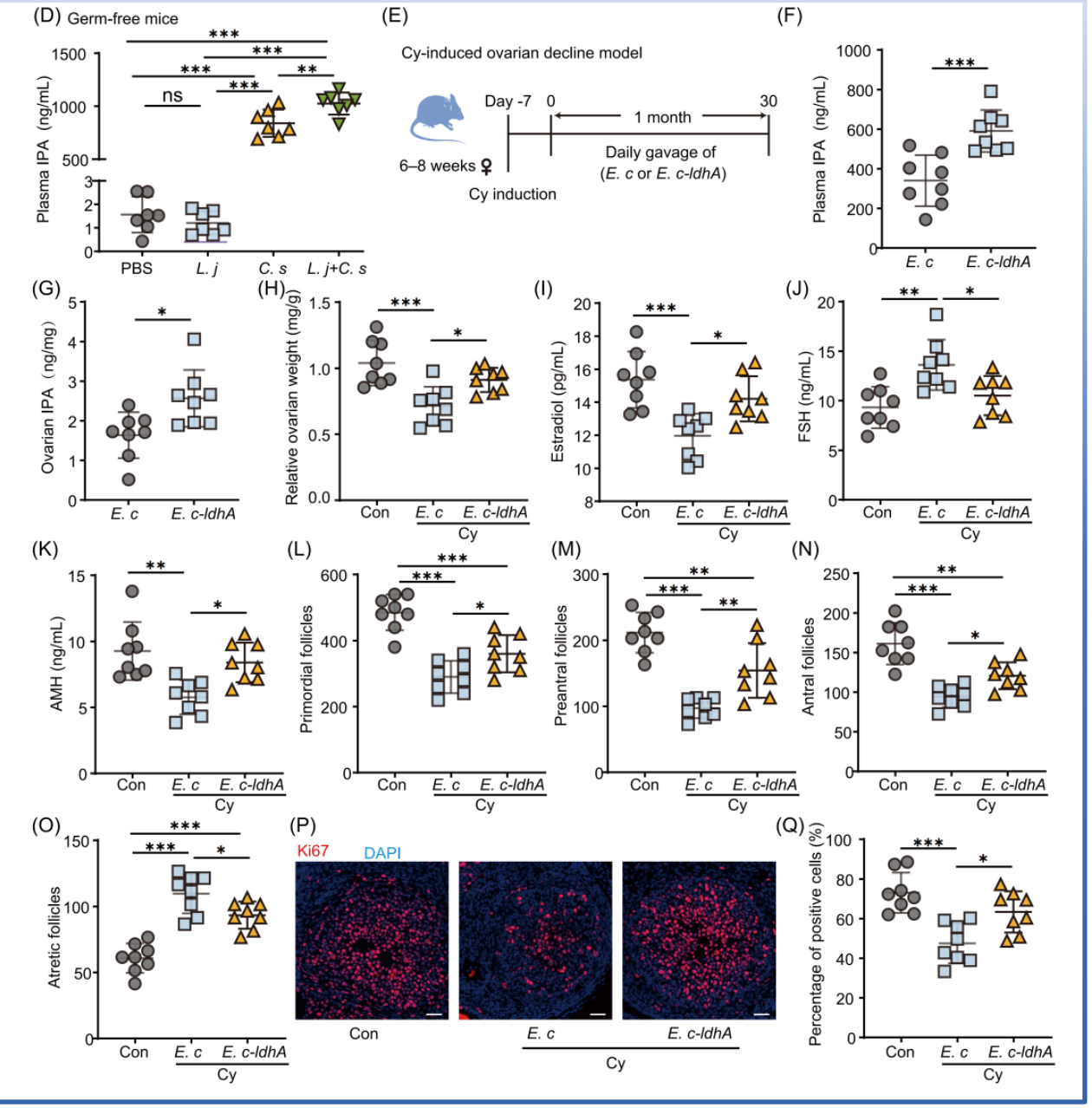
Tryptophan-dependent: On a tryptophan-free diet, *L. johnsonii* no longer raises ovarian weight or restores hormones.

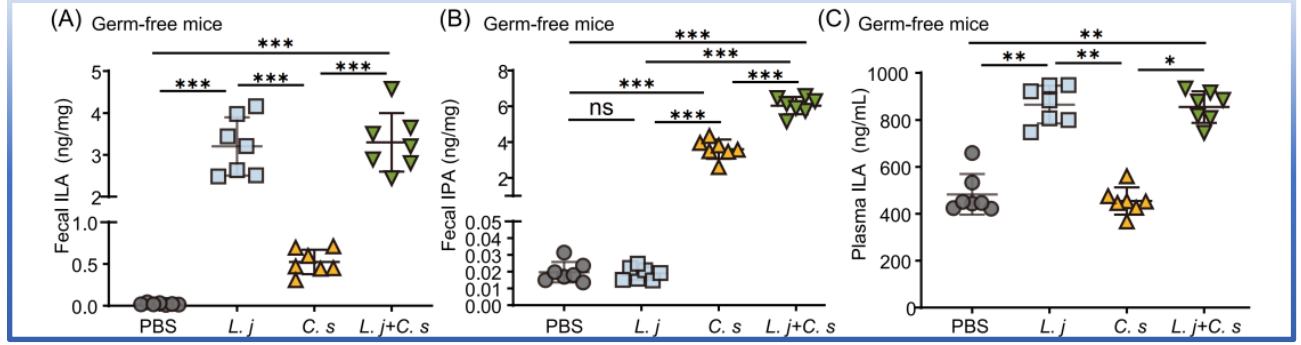
Candidate screening: IPYA, ILA and IPA rise in plasma; only ILA and IPA are detected in ovary, with **IPA showing the largest increase**.

Add-back: ILA or IPA both raise ovarian weight; but **IPA fully corrects E2/FSH/AMH** and reduces atretic follicles, outperforming ILA.



LdhA is the key enzyme for *L. johnsonii* to attenuate ovarian decline





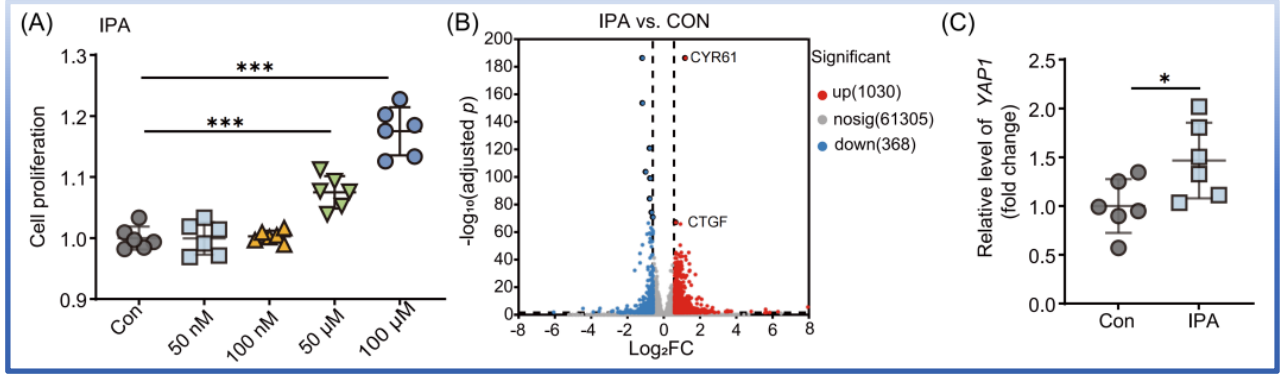
Key findings

Two-step metabolism: In germ-free mice, *L. johnsonii* alone produces ILA; IPA requires co-colonization with spore-forming commensals.

Key enzyme: Genome and protein alignment identify ldhA as the ILA-synthesizing enzyme; *L. johnsonii* shows the highest ILA output among six species of the genus *Lactobacillus*.

Genetic rescue: *E. coli-ldhA* gavage raises plasma and ovarian IPA in Cy-mice, reduces damage and promotes follicle proliferation.

IPA enhances granulosa cell proliferation via the regulation of AhR/YAP



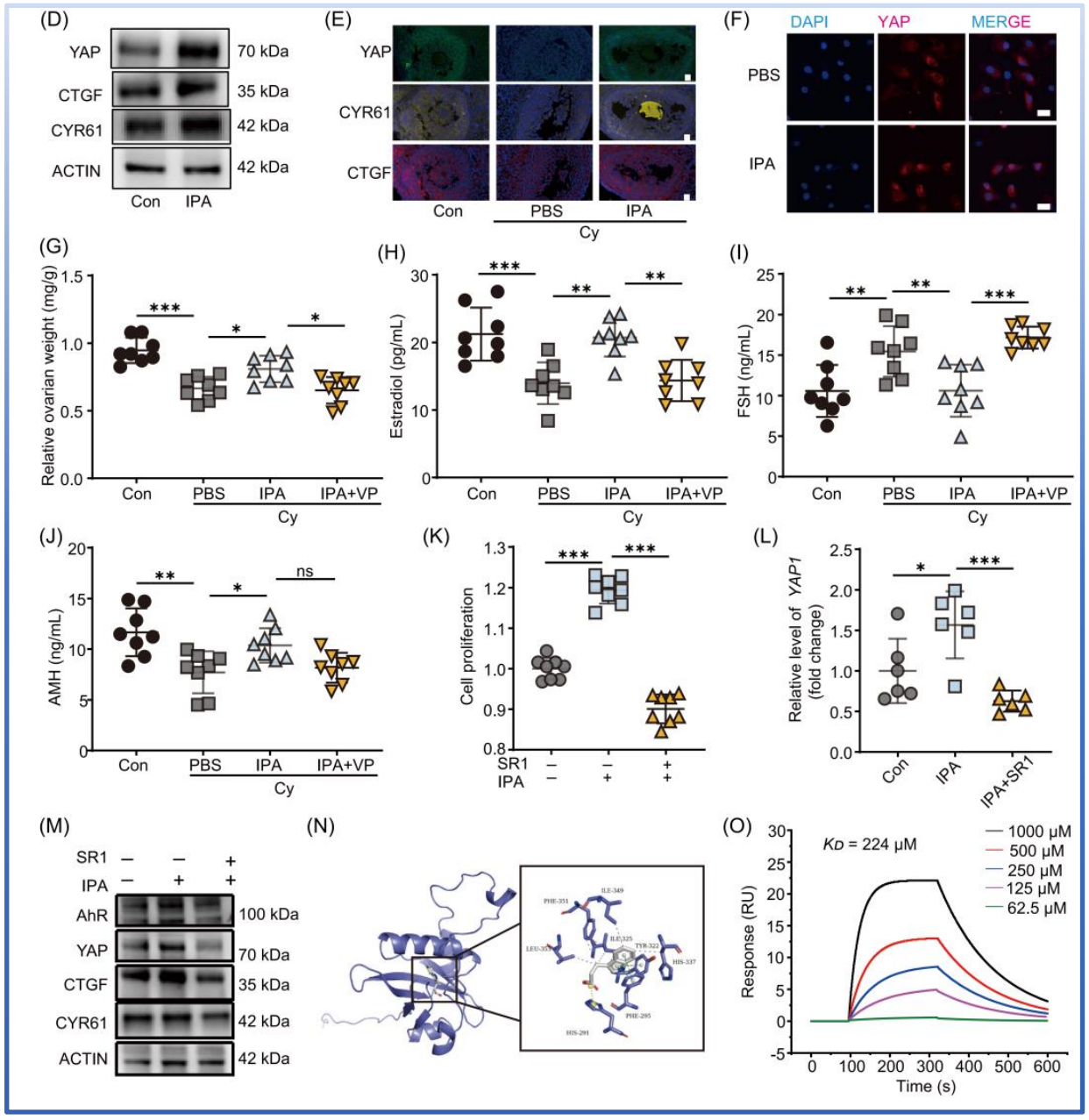
Evidence chain

Phenotype: IPA dose-dependently promotes KGN proliferation and suppresses apoptosis; RNA-seq reveals YAP targets *CTGF*/*CYR61* altered.

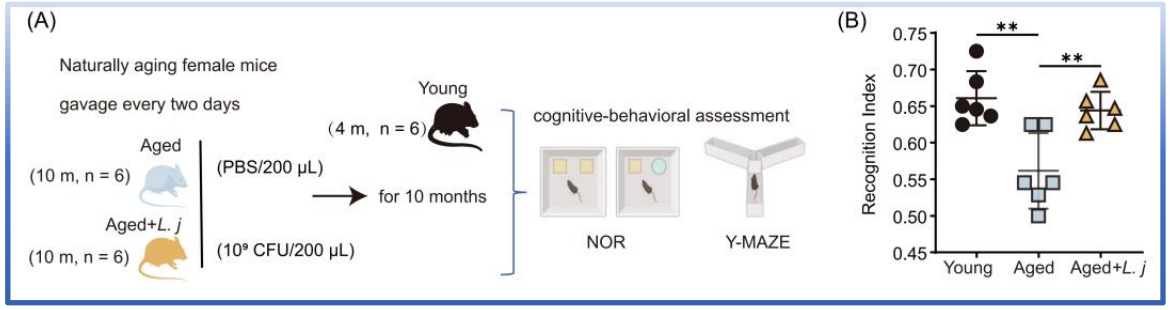
Nuclear translocation: IPA promotes YAP nuclear entry; YAP inhibitor verteporfin (VP) abolishes IPA effects *in vitro* and *in vivo*.

Upstream receptor: AhR inhibitor SR1 blocks IPA effects.

Direct binding: Docking (PDB:7ZUB) + SPR show IPA binds AhR domain D.



L. johnsonii improves healthspan in aging female mice and humans

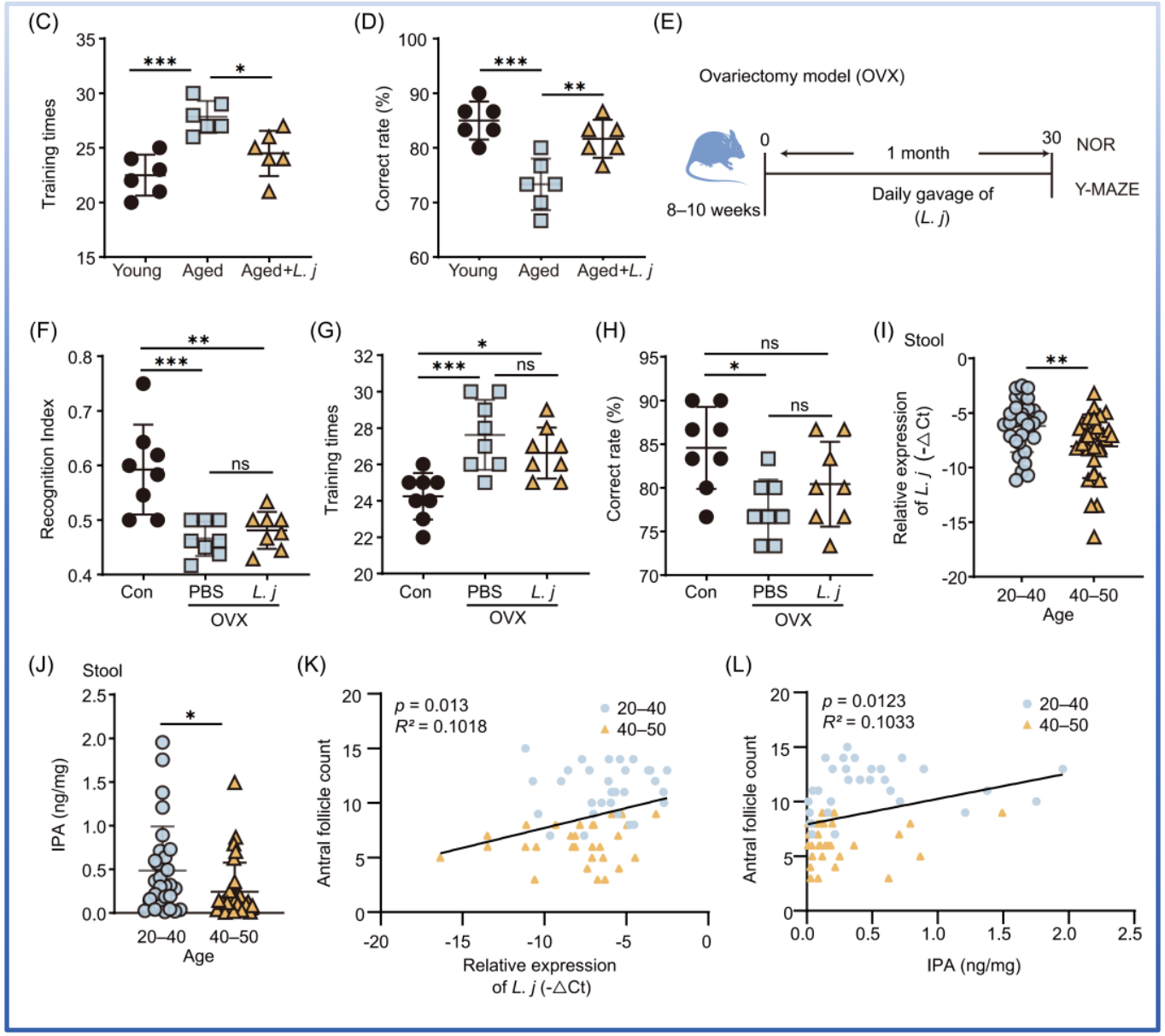


Key findings

Cognition depends on ovary: NOR and Y-maze show *L. johnsonii* alleviates age-related cognitive decline; effect disappears in OVX mice.

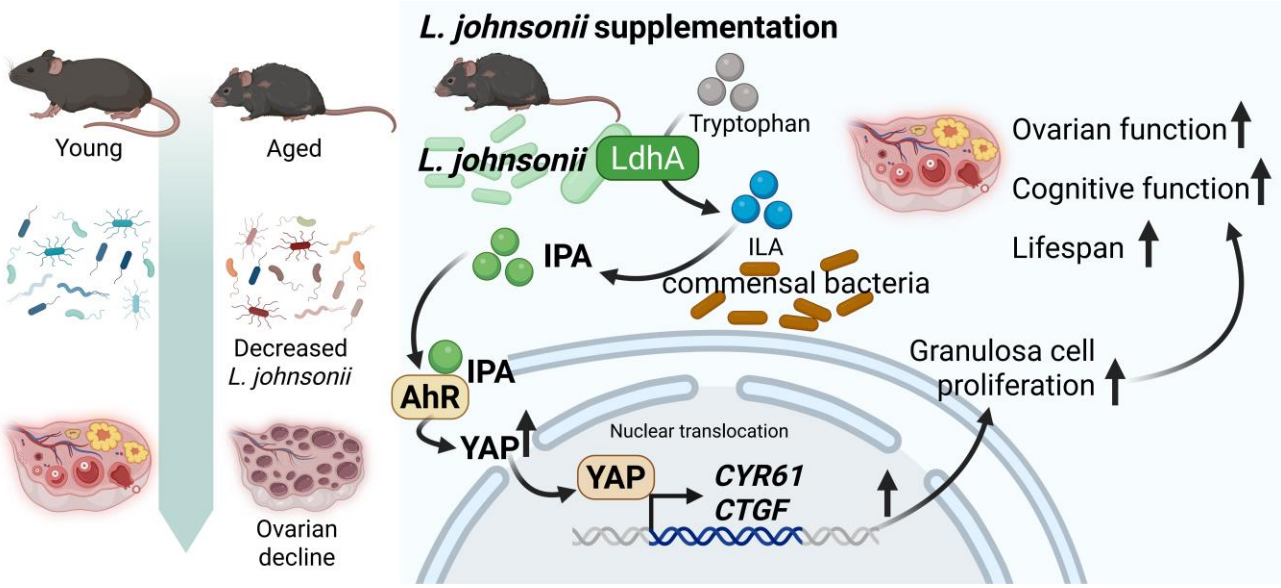
Human trend: Women aged 40–50 carry less fecal *L. johnsonii* and IPA than those aged 20–40; both inversely correlate with age.

Clinical correlation: Fecal *L. johnsonii* abundance and IPA both positively correlate with antral follicle count (AFC), supporting translational potential.



Summary

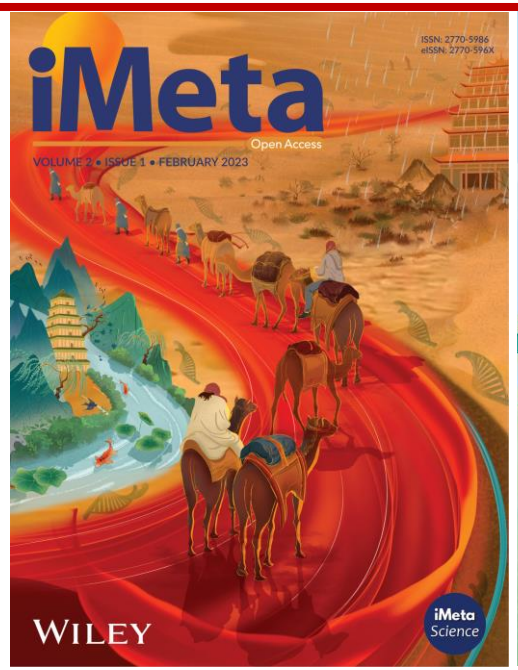
- Gut commensal *Lactobacillus johnsonii* (*L. johnsonii*) decreases with ovarian aging, and its supplementation ameliorates ovarian dysfunction in two mouse models.
- Microbial-derived indole-3-propionic acid (IPA) drives granulosa cell proliferation via the AhR-YAP signaling cascade.
- Fecal *L. johnsonii* and IPA levels positively correlate with ovarian function, supporting a gut-ovary axis probiotic strategy against female reproductive aging.

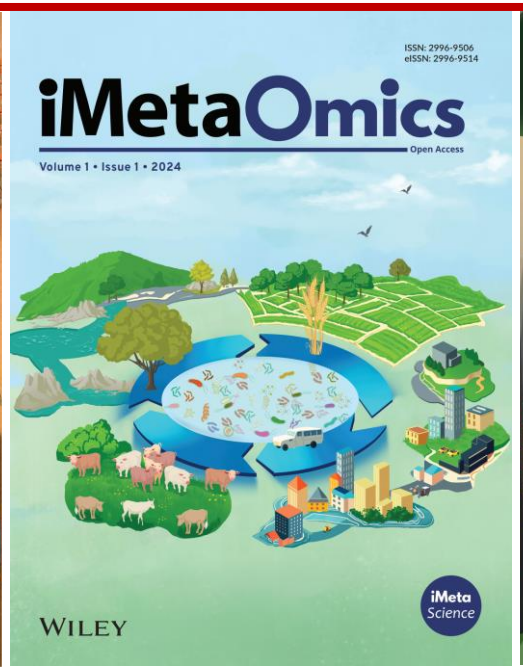


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